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1 [M]----- 1720440 1 [M]RAPGAGTASVASLALLWFLGLPWTWSAAA GI 2612939			
2 ----- 1720440 31 A P C V Y V G G G G W R F L R I V C K T A R R D L F G L S V GI 2612939			
2 ----- 1720440 61 L I R V R L E L R R H R R A G D T I P C I F Q A V A R R Q P GI 2612939			
2 ----- 1720440 91 E R L A L V D A S S G I C W T F A Q L D T Y S N A V A N L P GI 2612939			
2 ----- [E N R R E F V G L W L G M A K] 1720440 121 R Q L G F A P G D V V A V F L [E G R F E F V G L W L G L A K] GI 2612939			
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(57) Abstract  The invention provides human membrane transport proteins (MTRP) and polynucleotides which identify and encode MTRP. The invention also provides expression vectors, host cells, antibodies, agonists, and antagonists. The invention also provides methods for diagnosing, treating, or preventing disorders associated with expression of MTRP.			

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**MEMBRANE TRANSPORT PROTEINS****TECHNICAL FIELD**

This invention relates to nucleic acid and amino acid sequences of membrane transport  
5 proteins and to the use of these sequences in the diagnosis, treatment, and prevention of membrane  
transport disorders; immune/inflammatory disorders; and cell proliferative disorders including cancer.

**BACKGROUND OF THE INVENTION**

Eukaryotic cells are bound by a lipid bilayer membrane and subdivided into functionally  
10 distinct, membrane bound compartments. The membranes maintain essential differences between the  
cytosol, the extracellular environment, and the contents of intracellular organelles such as the Golgi or  
the endoplasmic reticulum. As lipid membranes are highly impermeable to most polar molecules,  
transport of essential nutrients; metal ions such as  $K^+$ ,  $NH_4^+$ ,  $P_i$ ,  $SO_4^{2-}$ ; sugars; vitamins; metabolic  
waste products; cell signaling molecules; drugs; peptides; and proteins and other macromolecules  
15 across lipid membranes and between organelles must be mediated by a variety of transport molecules.  
Many transport mechanisms are substrate specific, with each transport protein carrying particular  
members of a molecular class, such as ions, sugars, or amino acids, across membranes. For example,  
amino acids are imported into cells via specific amino acid permeases.

Transport proteins are multi-pass transmembrane proteins, which either actively transport  
20 molecules across the membrane or passively allow them to cross. Active transport involves  
directional pumping of a solute across the membrane, usually against an electrochemical gradient.  
Active transport is tightly coupled to a source of metabolic energy, such as ATP hydrolysis or an  
electrochemically favorable ion gradient. Passive transport involves the movement of a solute down  
its electrochemical gradient. Transport proteins can be further classified as either carrier proteins or  
25 channel proteins. Carrier proteins, which can function in active or passive transport, bind to a specific  
solute to be transported and undergo a conformational change which transfers the bound solute across  
the membrane. Channel proteins, which only function in passive transport, form hydrophilic pores  
across the membrane. When the pores open, specific solutes, such as inorganic ions, pass through the  
membrane and down the electrochemical gradient of the solute.

30 Transport proteins play roles in antibiotic resistance, toxin secretion, ion balance, synaptic  
neurotransmission, kidney function, intestinal absorption, tumor growth, and other diverse cell  
functions (Griffith, J. and C. Sansom (1998) The Transporter Facts Book, Academic Press, San Diego  
CA, pp. 3-29). A variety of human inherited diseases are caused by mutation of transport proteins.  
For example, cystinuria is an inherited disease that results from the inability to transport cystine, the

disulfide-linked dimer of cysteine, from the urine into the blood. Accumulation of cystine in the urine leads to the formation of cystine stones in the kidneys. Also, many transport proteins are composed of subunits that may confer specificity for the tissue in which the transport mechanism functions, and are therefore associated with tissue-specific disorders. Examples of transport proteins include

5 facilitative transporters, the secondary active symporters and antiporters driven by ion gradients, and active ATP binding cassette transporters involved in multiple-drug resistance and targeting of antigenic peptides to MHC Class I molecules, and the E1-E2 cation transport ATPases.

Carrier proteins which transport a single solute from one side of the membrane to the other are called uniporters. In contrast, coupled transporters link the transfer of one solute with

10 simultaneous or sequential transfer of a second solute, either in the same direction (symport) or in the opposite direction (antiport). For example, intestinal and kidney epithelium contains a variety of symporter systems wherein the movement of sodium into the cell down its electrochemical gradient co-transport a second solute into the cell. The sodium gradient that provides the driving force for solute uptake is maintained by the ubiquitous  $\text{Na}^+/\text{K}^+$  ATPase. Sodium-coupled transporters include

15 the mammalian glucose transporter (SGLT1), iodide transporter (NIS), and multivitamin transporter (SMVT). These three transporters have twelve putative transmembrane segments, extracellular glycosylation sites, and cytoplasmically-oriented N- and C-termini. NIS plays a crucial role in the evaluation, diagnosis, and treatment of various thyroid pathologies because it is the molecular basis for radioiodide thyroid-imaging techniques and for specific targeting of radioisotopes to the thyroid

20 gland (Levy, O. et al. (1997) Proc. Natl. Acad. Sci. USA 94:5568-5573). SMVT is expressed in the intestinal mucosa, kidney, and placenta, and is implicated in the transport of the water-soluble vitamins, e.g., biotin and pantothenate (Prasad, P.D. et al. (1998) J. Biol. Chem. 273:7501-7506).

The largest and most diverse family of transport proteins is the ATP-binding cassette (ABC) transporters. As a family, ABC transporters can transport substances that differ markedly in chemical

25 structure and size, ranging from small molecules such as ions, sugars, amino acids, peptides, and phospholipids, to lipopeptides, large proteins, and complex hydrophobic drugs. Each ABC transporter consists of four modules: two nucleotide-binding domains (NBDs), which hydrolyze ATP to supply the energy required for transport; and two membrane-spanning domains (MSDs), which may form membrane channels. The NBDs consist of approximately two hundred conserved amino

30 acid residues while the MSDs each contain six putative transmembrane segments. (See, e.g., Saurin, W. et al. (1994) Mol. Microbiol. 12:993-1004; Shani, N. et al. (1996) J. Biol. Chem. 271:8725-8730; Koster, W. and B. Bohm (1992) Mol. Gen. Genet. 232:399-407.) The four ABC transporter modules may be encoded by a single gene, as is the case for the cystic fibrosis transmembrane conductance regulator (CFTR), or by separate genes. When encoded by separate genes, each gene product

contains a single NBD and MSD. These "half-molecules" form homo- and heterodimers, such as Tap1 and Tap2, the endoplasmic reticulum-based major histocompatibility (MHC) peptide transport system associated with antigen processing (Androlewicz, M.J. et al. (1994) Proc. Natl. Acad. Sci. USA 91:12716-12720).

- 5        Several genetic diseases are attributed to defects in ABC transporters, including the following diseases and their corresponding proteins: cystic fibrosis (CFTR, an ion channel; Welsh, M.J. and A.E. Smith (1993) Cell 73:1251-1254); X-linked adrenoleukodystrophy, an inborn error of peroxisomal  $\beta$ -oxidation of very long chain fatty acids (adrenoleukodystrophy protein, ALDP); Zellweger syndrome, an inborn error of peroxisome biogenesis (peroxisomal membrane protein-70, 10 PMP70); and hyperinsulinemic hypoglycemia (sulfonylurea receptor, SUR). The ABC transporters known as P-glycoproteins, or multidrug resistance (MDR) proteins, are associated with resistance to a wide range of hydrophobic drugs (MDR1; Gottesman, M.M. and I. Pastan (1993) Annu. Rev. Biochem. 62:385-427) or with phosphatidylcholine transport (MDR2; Ruetz, S. and P. Gros (1994) Cell 77:1071-1081). MDR is common in cancer cells, and contributes to low efficacy or failure of 15 chemotherapy (Taglicht, D. and S. Michaelis (1998) Methods Enzymol. 292:131-163). MDR is mediated by transporters, e.g., P-glycoproteins or the multidrug resistance-associated protein MRP, that normally function in the liver, intestines, and kidney to move toxic substances from the cytosol into the bile, intestinal lumen, or urine. In cancerous cells, these transporters extrude chemotherapeutic agents into the extracellular space, thereby conferring drug resistance. Recently, an 20 ABC transporter-type protein was isolated from a human leukemia cell line. This transporter, termed the anthracycline resistance associated protein (GI 1279457, SEQ ID NO:42), is overexpressed in a multidrug resistant leukemia cell sub-line, and has sequence homology with other multidrug-resistance associated proteins including MRP (Longhurst, T.J. et al. (1996) Br. J. Cancer 74:1331-1335).
- 25        Transport of fatty acids across the plasma membrane can occur by diffusion, a high capacity, low affinity process. However, under normal physiological conditions a significant fraction of fatty acid transport appears to occur via a high affinity, low capacity protein-mediated transport process. Fatty acid transport protein (FATP), an integral membrane protein with four transmembrane segments, is expressed in tissues exhibiting high levels of plasma membrane fatty acid flux, such as 30 muscle, heart, and adipose. Expression of FATP is upregulated in 3T3-L1 cells during adipose conversion, and expression in COS7 fibroblasts elevates the cells' uptake of long-chain fatty acids. Expression studies suggest a role for FATP in lipid metabolism, obesity, and type II diabetes mellitus (Hui, T.Y. et al. (1998) J. Biol. Chem. 273:27420-27429).

E1-E2 (or P-type) ATPases constitute a superfamily of cation transporters present in both

prokaryotes and eukaryotes that mediate membrane flux of all biologically relevant cations. These ATPases are postulated to exist in two different conformational states, designated E1 and E2, during the course of the ATP hydrolysis reaction, and to conserve the energy from ATP hydrolysis in the form of an acyl phosphate, primarily an aspartyl phosphate. Members of this family are divided into  
5 four major groups; the  $\text{Ca}^{+2}$ -transporting ATPases,  $\text{Na}^{+}/\text{K}^{+}$ -and gastric  $\text{H}^{+}/\text{K}^{+}$ -transporting ATPases, plasma membrane  $\text{H}^{+}$ -transporting ATPases (proton pumps), and the bacterial P-type ATPases (BLOCKS: BL00154, P-type cation-transporting ATPase superfamily signature).

The metabolism of amino acids is complex and highly regulated. While cells are capable of creating most amino acids de novo, the import of amino acids into cells via specific amino acid  
10 permease proteins is vital for maintaining the appropriate and complete availability of all necessary amino acids. This is particularly important during cell proliferation and differentiation. In addition to their role as protein building blocks, amino acids also serve as precursors for a variety of other important macromolecules. For example, the hormone thyroxine, the pigment melanin, and the neurotransmitters histamine, epinephrine, and serotonin are produced from various amino acid  
15 precursors, including histidine, tyrosine, and tryptophan. A component of sphingolipid formation, sphingosine, is derived from serine. Porphyrin rings, which are components of heme molecules, use glycine as a nitrogen donor. Significant portions of the ring structures of purines and pyrimidines, components of nucleic acids, are formed from the breakdown of numerous amino acids. Amino acids are also important in energy metabolism. Unlike fatty acids and glucose, amino acids cannot be  
20 stored in the cell, so excess amino acids are fed into the citric acid cycle to produce energy molecules including fatty acids, ketone bodies, and glucose. Thus, precise control of amino acid metabolism is extremely important to both proliferating and non-proliferating cells.

The E16 gene, cloned from human peripheral blood lymphocytes, encodes a 241 amino acid integral membrane protein with multiple predicted transmembrane domains (Gaugitsch, H.W. et al.  
25 (1992) J. Biol. Chem. 267:11267-11273). E16 gene expression is closely linked to cellular activation and division. In myeloid and lymphoid cells, E16 transcripts are rapidly induced and rapidly degraded after stimulation. This pattern of expression resembles the kinetics seen for proto-oncogenes and lymphokines in the T cell system. Elevated levels of E16 expression were detected in colonic, gastric, and breast adenocarcinomas, and in lymphoma, while little or no E16 expression was  
30 detected in normal (non-cancerous) human tissues such as adult brain, lung, liver, colon, esophagus, stomach, or kidney, nor in four-month fetal brain, lung, liver, or kidney (Wolf, D.A. et al. (1996) Cancer Res. 56:5012-5022; Gaugitsch et al., *supra*). E16 was detected in every cell line tested. Its presence in rapidly dividing cell lines and its absence in human tissues with low proliferative potential suggest that E16 is directly involved in the cell division process, where it helps provide important

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building blocks for energy metabolism, biochemical synthetic pathways, and protein synthesis.

Post-translational modification of polypeptides occurs in the lumen of the Golgi apparatus. Such modifications include, for example, the addition of sugar molecules by enzymes such as N-acetylglucosaminyltransferase, to produce glycoproteins. The sugar-donating molecules in this reaction are typically nucleotide sugars, such as uridine diphosphate-galactose (UDP-Gal). UDP-Gal and other nucleotide sugars are transported from the cytosol into the Golgi apparatus by specific transporter molecules. The availability of these nucleotide sugars can regulate which glycoproteins are synthesized, and therefore has a significant impact on cellular function (Toma, L. et al. (1996) J. Biol. Chem. 271:3897-3901; Guillen, E. et al. (1998) Proc. Natl. Acad. Sci. USA 95:7888-7892).

The discovery of new membrane transport proteins and the polynucleotides encoding them satisfies a need in the art by providing new compositions which are useful in the diagnosis, prevention, and treatment of membrane transport disorders; immune/inflammatory disorders; and cell proliferative disorders including cancer.

## SUMMARY OF THE INVENTION

The invention features substantially purified polypeptides, membrane transport proteins, referred to collectively as "MTRP" and individually as "MTRP-1," "MTRP-2," "MTRP-3," "MTRP-4," "MTRP-5," "MTRP-6," "MTRP-7," "MTRP-8," "MTRP-9," "MTRP-10," "MTRP-11," "MTRP-12," "MTRP-13," "MTRP-14," "MTRP-15," "MTRP-16," and "MTRP-17." In one aspect, the invention provides a substantially purified polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-17 and fragments thereof. The invention also includes a polypeptide comprising an amino acid sequence that differs by one or more conservative amino acid substitutions from an amino acid sequence selected from the group consisting of SEQ ID NO:1-17.

The invention further provides a substantially purified variant having at least 90% amino acid identity to at least one of the amino acid sequences selected from the group consisting of SEQ ID NO:1-17 and fragments thereof. The invention also provides an isolated and purified polynucleotide encoding the polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-17 and fragments thereof. The invention also includes an isolated and purified polynucleotide variant having at least 90% polynucleotide sequence identity to the polynucleotide encoding the polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-17 and fragments thereof.

Additionally, the invention provides an isolated and purified polynucleotide which hybridizes under stringent conditions to the polynucleotide encoding the polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-17 and fragments thereof. The

invention also provides an isolated and purified polynucleotide having a sequence which is complementary to the polynucleotide encoding the polypeptide comprising the amino acid sequence selected from the group consisting of SEQ ID NO:1-17 and fragments thereof.

The invention also provides a method for detecting a polynucleotide in a sample containing nucleic acids, the method comprising the steps of: (a) hybridizing the complement of the polynucleotide sequence to at least one of the polynucleotides of the sample, thereby forming a hybridization complex; and (b) detecting the hybridization complex, wherein the presence of the hybridization complex correlates with the presence of a polynucleotide in the sample. In one aspect, the method further comprises amplifying the polynucleotide prior to hybridization.

The invention also provides an isolated and purified polynucleotide comprising a polynucleotide sequence selected from the group consisting of SEQ ID NO:18-34 and fragments thereof. The invention further provides an isolated and purified polynucleotide variant having at least 90% polynucleotide sequence identity to the polynucleotide sequence selected from the group consisting of SEQ ID NO:18-34 and fragments thereof. The invention also provides an isolated and purified polynucleotide having a sequence which is complementary to the polynucleotide comprising a polynucleotide sequence selected from the group consisting of SEQ ID NO:18-34 and fragments thereof.

The invention further provides an expression vector containing at least a fragment of the polynucleotide encoding the polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-17. In another aspect, the expression vector is contained within a host cell.

The invention also provides a method for producing a polypeptide, the method comprising the steps of: (a) culturing the host cell containing an expression vector containing a polynucleotide of the invention under conditions suitable for the expression of the polypeptide; and (b) recovering the polypeptide from the host cell culture.

The invention also provides a pharmaceutical composition comprising a substantially purified polypeptide having the amino acid sequence selected from the group consisting of SEQ ID NO:1-17 and fragments thereof, in conjunction with a suitable pharmaceutical carrier.

The invention further includes a purified antibody which binds to a polypeptide selected from the group consisting of SEQ ID NO:1-17 and fragments thereof. The invention also provides a purified agonist and a purified antagonist to the polypeptide.

The invention also provides a method for treating or preventing a disorder associated with decreased expression or activity of MTRP, the method comprising administering to a subject in need of such treatment an effective amount of a pharmaceutical composition comprising a substantially



purified polypeptide having the amino acid sequence selected from the group consisting of SEQ ID NO:1-17 and fragments thereof, in conjunction with a suitable pharmaceutical carrier.

The invention also provides a method for treating or preventing a disorder associated with increased expression or activity of MTRP, the method comprising administering to a subject in need of such treatment an effective amount of an antagonist of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-17 and fragments thereof.

### BRIEF DESCRIPTION OF THE FIGURES AND TABLES

Figures 1A, 1B, 1C, and 1D show the amino acid sequence alignment between MTRP-3 (Incyte Clone ID 1720440; SEQ ID NO:3) and mouse fatty acid transport protein (GI 2612939; SEQ ID NO:35), produced using the multisequence alignment program of LASERGENE software (DNASTAR, Madison WI).

Figures 2A, 2B, 2C, and 2D show the amino acid sequence alignment between MTRP-4 (Incyte Clone ID 2274290; SEQ ID NO:4) and Schistosoma mansoni SMDR1 (GI 425474; SEQ ID NO:36), produced using the multisequence alignment program of LASERGENE software (DNASTAR).

Figures 3A, 3B, 3C, and 3D show the amino acid sequence alignment between MTRP-5 (Incyte Clone ID 2740029; SEQ ID NO:5) and rat sodium-dependent multivitamin transporter (GI 3015617; SEQ ID NO:37), produced using the multisequence alignment program of LASERGENE software (DNASTAR).

Table 1 shows polypeptide and nucleotide sequence identification numbers (SEQ ID NOs), clone identification numbers (clone IDs), cDNA libraries, and cDNA fragments used to assemble full-length sequences encoding MTRP.

Table 2 shows features of each polypeptide sequence, including potential motifs, homologous sequences, and methods, algorithms, and searchable databases used for analysis of MTRP.

Table 3 shows the tissue-specific expression patterns of each nucleic acid sequence as determined by northern analysis; diseases, disorders, or conditions associated with these tissues; and the vector into which each cDNA was cloned.

Table 4 describes the tissues used to construct the cDNA libraries from which cDNA clones encoding MTRP were isolated.

Table 5 shows the tools, programs, and algorithms used to analyze MTRP, along with applicable descriptions, references, and threshold parameters.

### DESCRIPTION OF THE INVENTION

Before the present proteins, nucleotide sequences, and methods are described, it is understood that this invention is not limited to the particular machines, materials and methods described, as these may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims.

It must be noted that as used herein and in the appended claims, the singular forms "a," "an," and "the" include plural reference unless the context clearly dictates otherwise. Thus, for example, a reference to "a host cell" includes a plurality of such host cells, and a reference to "an antibody" is a reference to one or more antibodies and equivalents thereof known to those skilled in the art, and so forth.

Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any machines, materials, and methods similar or equivalent to those described herein can be used to practice or test the present invention, the preferred machines, materials and methods are now described. All publications mentioned herein are cited for the purpose of describing and disclosing the cell lines, protocols, reagents and vectors which are reported in the publications and which might be used in connection with the invention. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

#### DEFINITIONS

"MTRP" refers to the amino acid sequences of substantially purified MTRP obtained from any species, particularly a mammalian species, including bovine, ovine, porcine, murine, equine, and human, and from any source, whether natural, synthetic, semi-synthetic, or recombinant.

The term "agonist" refers to a molecule which intensifies or mimics the biological activity of MTRP. Agonists may include proteins, nucleic acids, carbohydrates, small molecules, or any other compound or composition which modulates the activity of MTRP either by directly interacting with MTRP or by acting on components of the biological pathway in which MTRP participates.

An "allelic variant" is an alternative form of the gene encoding MTRP. Allelic variants may result from at least one mutation in the nucleic acid sequence and may result in altered mRNAs or in polypeptides whose structure or function may or may not be altered. A gene may have none, one, or many allelic variants of its naturally occurring form. Common mutational changes which give rise to allelic variants are generally ascribed to natural deletions, additions, or substitutions of nucleotides. Each of these types of changes may occur alone, or in combination with the others, one or more times in a given sequence.

"Altered" nucleic acid sequences encoding MTRP include those sequences with deletions,

insertions, or substitutions of different nucleotides, resulting in a polypeptide the same as MTRP or a polypeptide with at least one functional characteristic of MTRP. Included within this definition are polymorphisms which may or may not be readily detectable using a particular oligonucleotide probe of the polynucleotide encoding MTRP, and improper or unexpected hybridization to allelic variants, with a locus other than the normal chromosomal locus for the polynucleotide sequence encoding MTRP. The encoded protein may also be "altered," and may contain deletions, insertions, or substitutions of amino acid residues which produce a silent change and result in a functionally equivalent MTRP. Deliberate amino acid substitutions may be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity, and/or the amphipathic nature of the residues, as long as the biological or immunological activity of MTRP is retained. For example, negatively charged amino acids may include aspartic acid and glutamic acid, and positively charged amino acids may include lysine and arginine. Amino acids with uncharged polar side chains having similar hydrophilicity values may include: asparagine and glutamine; and serine and threonine. Amino acids with uncharged side chains having similar hydrophilicity values may include: leucine, isoleucine, and valine; glycine and alanine; and phenylalanine and tyrosine.

The terms "amino acid" and "amino acid sequence" refer to an oligopeptide, peptide, polypeptide, or protein sequence, or a fragment of any of these, and to naturally occurring or synthetic molecules. Where "amino acid sequence" is recited to refer to an amino acid sequence of a naturally occurring protein molecule, "amino acid sequence" and like terms are not meant to limit the amino acid sequence to the complete native amino acid sequence associated with the recited protein molecule.

"Amplification" relates to the production of additional copies of a nucleic acid sequence. Amplification is generally carried out using polymerase chain reaction (PCR) technologies well known in the art.

The term "antagonist" refers to a molecule which inhibits or attenuates the biological activity of MTRP. Antagonists may include proteins such as antibodies, nucleic acids, carbohydrates, small molecules, or any other compound or composition which modulates the activity of MTRP either by directly interacting with MTRP or by acting on components of the biological pathway in which MTRP participates.

The term "antibody" refers to intact immunoglobulin molecules as well as to fragments thereof, such as Fab, F(ab')<sub>2</sub>, and Fv fragments, which are capable of binding an epitopic determinant. Antibodies that bind MTRP polypeptides can be prepared using intact polypeptides or using fragments containing small peptides of interest as the immunizing antigen. The polypeptide or oligopeptide used to immunize an animal (e.g., a mouse, a rat, or a rabbit) can be derived from the

translation of RNA, or synthesized chemically, and can be conjugated to a carrier protein if desired. Commonly used carriers that are chemically coupled to peptides include bovine serum albumin, thyroglobulin, and keyhole limpet hemocyanin (KLH). The coupled peptide is then used to immunize the animal.

5       The term "antigenic determinant" refers to that region of a molecule (i.e., an epitope) that makes contact with a particular antibody. When a protein or a fragment of a protein is used to immunize a host animal, numerous regions of the protein may induce the production of antibodies which bind specifically to antigenic determinants (particular regions or three-dimensional structures on the protein). An antigenic determinant may compete with the intact antigen (i.e., the immunogen  
10       used to elicit the immune response) for binding to an antibody.

      The term "antisense" refers to any composition containing a nucleic acid sequence which is complementary to the "sense" strand of a specific nucleic acid sequence. Antisense molecules may be produced by any method including synthesis or transcription. Once introduced into a cell, the complementary nucleotides combine with natural sequences produced by the cell to form duplexes  
15       and to block either transcription or translation. The designation "negative" or "minus" can refer to the antisense strand, and the designation "positive" or "plus" can refer to the sense strand.

      The term "biologically active" refers to a protein having structural, regulatory, or biochemical functions of a naturally occurring molecule. Likewise, "immunologically active" refers to the capability of the natural, recombinant, or synthetic MTRP, or of any oligopeptide thereof, to induce a  
20       specific immune response in appropriate animals or cells and to bind with specific antibodies.

      The terms "complementary" and "complementarity" refer to the natural binding of polynucleotides by base pairing. For example, the sequence "5' A-G-T 3'" bonds to the complementary sequence "3' T-C-A 5'." Complementarity between two single-stranded molecules may be "partial," such that only some of the nucleic acids bind, or it may be "complete," such that  
25       total complementarity exists between the single stranded molecules. The degree of complementarity between nucleic acid strands has significant effects on the efficiency and strength of the hybridization between the nucleic acid strands. This is of particular importance in amplification reactions, which depend upon binding between nucleic acid strands, and in the design and use of peptide nucleic acid (PNA) molecules.

30       A "composition comprising a given polynucleotide sequence" and a "composition comprising a given amino acid sequence" refer broadly to any composition containing the given polynucleotide or amino acid sequence. The composition may comprise a dry formulation or an aqueous solution. Compositions comprising polynucleotide sequences encoding MTRP or fragments of MTRP may be employed as hybridization probes. The probes may be stored in freeze-dried form and may be

associated with a stabilizing agent such as a carbohydrate.. In hybridizations, the probe may be deployed in an aqueous solution containing salts (e.g., NaCl), detergents (e.g., sodium dodecyl sulfate; SDS), and other components (e.g., Denhardt's solution, dry milk, salmon sperm DNA, etc.).

"Consensus sequence" refers to a nucleic acid sequence which has been resequenced to resolve uncalled bases, extended using the XL-PCR kit (Perkin-Elmer, Norwalk CT) in the 5' and/or the 3' direction, and resequenced, or which has been assembled from the overlapping sequences of one or more Incyte Clones and, in some cases, one or more public domain ESTs, using a computer program for fragment assembly, such as the GELVIEW fragment assembly system (GCG, Madison WI). Some sequences have been both extended and assembled to produce the consensus sequence.

"Conservative amino acid substitutions" are those substitutions that, when made, least interfere with the properties of the original protein, i.e., the structure and especially the function of the protein is conserved and not significantly changed by such substitutions. The table below shows amino acids which may be substituted for an original amino acid in a protein and which are regarded as conservative amino acid substitutions.

	Original Residue	Conservative Substitution
15	Ala	Gly, Ser
	Arg	His, Lys
	Asn	Asp, Gln, His
	Asp	Asn, Glu
20	Cys	Ala, Ser
	Gln	Asn, Glu, His
	Glu	Asp, Gln, His
	Gly	Ala
	His	Asn, Arg, Gln, Glu
25	Ile	Leu, Val
	Leu	Ile, Val
	Lys	Arg, Gln, Glu
	Met	Leu, Ile
	Phe	His, Met, Leu, Trp, Tyr
30	Ser	Cys, Thr
	Thr	Ser, Val
	Trp	Phe, Tyr
	Tyr	His, Phe, Trp
35	Val	Ile, Leu, Thr

Conservative amino acid substitutions generally maintain (a) the structure of the polypeptide backbone in the area of the substitution, for example, as a beta sheet or alpha helical conformation, (b) the charge or hydrophobicity of the molecule at the site of the substitution, and/or (c) the bulk of the side chain.

A "deletion" refers to a change in the amino acid or nucleotide sequence that results in the absence of one or more amino acid residues or nucleotides.

The term "derivative" refers to the chemical modification of a polypeptide sequence, or a polynucleotide sequence. Chemical modifications of a polynucleotide sequence can include, for example, replacement of hydrogen by an alkyl, acyl, hydroxyl, or amino group. A derivative polynucleotide encodes a polypeptide which retains at least one biological or immunological function of the natural molecule. A derivative polypeptide is one modified by glycosylation, pegylation, or any similar process that retains at least one biological or immunological function of the polypeptide from which it was derived.

A "fragment" is a unique portion of MTRP or the polynucleotide encoding MTRP which is identical in sequence to but shorter in length than the parent sequence. A fragment may comprise up to the entire length of the defined sequence, minus one nucleotide/amino acid residue. For example, a fragment may comprise from 5 to 1000 contiguous nucleotides or amino acid residues. A fragment used as a probe, primer, antigen, therapeutic molecule, or for other purposes, may be at least 5, 10, 15, 20, 25, 30, 40, 50, 60, 75, 100, 150, 250 or at least 500 contiguous nucleotides or amino acid residues in length. Fragments may be preferentially selected from certain regions of a molecule. For example, a polypeptide fragment may comprise a certain length of contiguous amino acids selected from the first 250 or 500 amino acids (or first 25% or 50% of a polypeptide) as shown in a certain defined sequence. Clearly these lengths are exemplary, and any length that is supported by the specification, including the Sequence Listing, tables, and figures, may be encompassed by the present embodiments.

A fragment of SEQ ID NO:18-34 comprises a region of unique polynucleotide sequence that specifically identifies SEQ ID NO:18-34, for example, as distinct from any other sequence in the same genome. A fragment of SEQ ID NO:18-34 is useful, for example, in hybridization and amplification technologies and in analogous methods that distinguish SEQ ID NO:18-34 from related polynucleotide sequences. The precise length of a fragment of SEQ ID NO:18-34 and the region of SEQ ID NO:18-34 to which the fragment corresponds are routinely determinable by one of ordinary skill in the art based on the intended purpose for the fragment.

A fragment of SEQ ID NO:1-17 is encoded by a fragment of SEQ ID NO:18-34. A fragment of SEQ ID NO:1-17 comprises a region of unique amino acid sequence that specifically identifies SEQ ID NO:1-17. For example, a fragment of SEQ ID NO:1-17 is useful as an immunogenic peptide for the development of antibodies that specifically recognize SEQ ID NO:1-17. The precise length of a fragment of SEQ ID NO:1-17 and the region of SEQ ID NO:1-17 to which the fragment corresponds are routinely determinable by one of ordinary skill in the art based on the intended purpose for the fragment.

The term "similarity" refers to a degree of complementarity. There may be partial similarity or complete similarity. The word "identity" may substitute for the word "similarity." A partially

complementary sequence that at least partially inhibits an identical sequence from hybridizing to a target nucleic acid is referred to as "substantially similar." The inhibition of hybridization of the completely complementary sequence to the target sequence may be examined using a hybridization assay (Southern or northern blot, solution hybridization, and the like) under conditions of reduced stringency. A substantially similar sequence or hybridization probe will compete for and inhibit the binding of a completely similar (identical) sequence to the target sequence under conditions of reduced stringency. This is not to say that conditions of reduced stringency are such that non-specific binding is permitted, as reduced stringency conditions require that the binding of two sequences to one another be a specific (i.e., a selective) interaction. The absence of non-specific binding may be tested by the use of a second target sequence which lacks even a partial degree of complementarity (e.g., less than about 30% similarity or identity). In the absence of non-specific binding, the substantially similar sequence or probe will not hybridize to the second non-complementary target sequence.

The phrases "percent identity" and "% identity," as applied to polynucleotide sequences, refer to the percentage of residue matches between at least two polynucleotide sequences aligned using a standardized algorithm. Such an algorithm may insert, in a standardized and reproducible way, gaps in the sequences being compared in order to optimize alignment between two sequences, and therefore achieve a more meaningful comparison of the two sequences.

Percent identity between polynucleotide sequences may be determined using the default parameters of the CLUSTAL V algorithm as incorporated into the MEGALIGN version 3.12e sequence alignment program. This program is part of the LASERGENE software package, a suite of molecular biological analysis programs (DNASTAR, Madison WI). CLUSTAL V is described in Higgins, D.G. and P.M. Sharp (1989) CABIOS 5:151-153 and in Higgins, D.G. et al. (1992) CABIOS 8:189-191. For pairwise alignments of polynucleotide sequences, the default parameters are set as follows: Ktuple=2, gap penalty=5, window=4, and "diagonals saved"=4. The "weighted" residue weight table is selected as the default. Percent identity is reported by CLUSTAL V as the "percent similarity" between aligned polynucleotide sequence pairs.

Alternatively, a suite of commonly used and freely available sequence comparison algorithms is provided by the National Center for Biotechnology Information (NCBI) Basic Local Alignment Search Tool (BLAST) (Altschul, S.F. et al. (1990) J. Mol. Biol. 215:403-410), which is available from several sources, including the NCBI, Bethesda, MD, and on the Internet at <http://www.ncbi.nlm.nih.gov/BLAST/>. The BLAST software suite includes various sequence analysis programs including "blastn," that is used to align a known polynucleotide sequence with other polynucleotide sequences from a variety of databases. Also available is a tool called "BLAST 2

Sequences" that is used for direct pairwise comparison of two nucleotide sequences. "BLAST 2 Sequences" can be accessed and used interactively at <http://www.ncbi.nlm.nih.gov/gorf/bl2.html>. The "BLAST 2 Sequences" tool can be used for both blastn and blastp (discussed below). BLAST programs are commonly used with gap and other parameters set to default settings. For example, to  
5 compare two nucleotide sequences, one may use blastn with the "BLAST 2 Sequences" tool Version 2.0.9 (May-07-1999) set at default parameters. Such default parameters may be, for example:

*Matrix: BLOSUM62*

*Reward for match: 1*

*Penalty for mismatch: -2*

10 *Open Gap: 5 and Extension Gap: 2 penalties*

*Gap x drop-off: 50*

*Expect: 10*

*Word Size: 11*

*Filter: on*

15 Percent identity may be measured over the length of an entire defined sequence, for example, as defined by a particular SEQ ID number, or may be measured over a shorter length, for example, over the length of a fragment taken from a larger, defined sequence, for instance, a fragment of at least 20, at least 30, at least 40, at least 50, at least 70, at least 100, or at least 200 contiguous nucleotides. Such lengths are exemplary only, and it is understood that any fragment length supported  
20 by the sequences shown herein, in the tables, figures, or Sequence Listing, may be used to describe a length over which percentage identity may be measured.

Nucleic acid sequences that do not show a high degree of identity may nevertheless encode similar amino acid sequences due to the degeneracy of the genetic code. It is understood that changes in a nucleic acid sequence can be made using this degeneracy to produce multiple nucleic acid  
25 sequences that all encode substantially the same protein.

The phrases "percent identity" and "% identity," as applied to polypeptide sequences, refer to the percentage of residue matches between at least two polypeptide sequences aligned using a standardized algorithm. Methods of polypeptide sequence alignment are well-known. Some alignment methods take into account conservative amino acid substitutions. Such conservative  
30 substitutions, explained in more detail above, generally preserve the hydrophobicity and acidity at the site of substitution, thus preserving the structure (and therefore function) of the polypeptide.

Percent identity between polypeptide sequences may be determined using the default parameters of the CLUSTAL V algorithm as incorporated into the MEGALIGN version 3.12e sequence alignment program (described and referenced above). For pairwise alignments of



polypeptide sequences using CLUSTAL V, the default parameters are set as follows: Ktuple=1, gap penalty=3, window=5, and "diagonals saved"=5. The PAM250 matrix is selected as the default residue weight table. As with polynucleotide alignments, the percent identity is reported by CLUSTAL V as the "percent similarity" between aligned polypeptide sequence pairs.

- 5 Alternatively the NCBI BLAST software suite may be used. For example, for a pairwise comparison of two polypeptide sequences, one may use the "BLAST 2 Sequences" tool Version 2.0.9 (May-07-1999) with blastp set at default parameters. Such default parameters may be, for example:

*Matrix: BLOSUM62*

*Open Gap: 11 and Extension Gap: 1 penalties*

10 *Gap x drop-off: 50*

*Expect: 10*

*Word Size: 3*

*Filter: on*

- Percent identity may be measured over the length of an entire defined polypeptide sequence, for example, as defined by a particular SEQ ID number, or may be measured over a shorter length, for example, over the length of a fragment taken from a larger, defined polypeptide sequence, for instance, a fragment of at least 15, at least 20, at least 30, at least 40, at least 50, at least 70 or at least 150 contiguous residues. Such lengths are exemplary only, and it is understood that any fragment length supported by the sequences shown herein, in the tables, figures or Sequence Listing, may be used to describe a length over which percentage identity may be measured.
- 15  
20

"Human artificial chromosomes" (HACs) are linear microchromosomes which may contain DNA sequences of about 6 kb to 10 Mb in size, and which contain all of the elements required for stable mitotic chromosome segregation and maintenance.

- The term "humanized antibody" refers to antibody molecules in which the amino acid sequence in the non-antigen binding regions has been altered so that the antibody more closely resembles a human antibody, and still retains its original binding ability.
- 25

- "Hybridization" refers to the process by which a polynucleotide strand anneals with a complementary strand through base pairing under defined hybridization conditions. Specific hybridization is an indication that two nucleic acid sequences share a high degree of identity. Specific hybridization complexes form under permissive annealing conditions and remain hybridized after the "washing" step(s). The washing step(s) is particularly important in determining the stringency of the hybridization process, with more stringent conditions allowing less non-specific binding, i.e., binding between pairs of nucleic acid strands that are not perfectly matched. Permissive conditions for annealing of nucleic acid sequences are routinely determinable by one of ordinary skill in the art and
- 30

may be consistent among hybridization experiments, whereas wash conditions may be varied among experiments to achieve the desired stringency, and therefore hybridization specificity. Permissive annealing conditions occur, for example, at 68°C in the presence of about 6 x SSC, about 1% (w/v) SDS, and about 100 µg/ml denatured salmon sperm DNA.

5 Generally, stringency of hybridization is expressed, in part, with reference to the temperature under which the wash step is carried out. Generally, such wash temperatures are selected to be about 5°C to 20°C lower than the thermal melting point ( $T_m$ ) for the specific sequence at a defined ionic strength and pH. The  $T_m$  is the temperature (under defined ionic strength and pH) at which 50% of the target sequence hybridizes to a perfectly matched probe. An equation for calculating  $T_m$  and  
10 conditions for nucleic acid hybridization are well known and can be found in Sambrook et al., 1989, Molecular Cloning: A Laboratory Manual, 2<sup>nd</sup> ed., vol. 1-3, Cold Spring Harbor Press, Plainview NY; specifically see volume 2, chapter 9.

High stringency conditions for hybridization between polynucleotides of the present invention include wash conditions of 68°C in the presence of about 0.2 x SSC and about 0.1% SDS, for 1 hour.  
15 Alternatively, temperatures of about 65°C, 60°C, 55°C, or 42°C may be used. SSC concentration may be varied from about 0.1 to 2 x SSC, with SDS being present at about 0.1%. Typically, blocking reagents are used to block non-specific hybridization. Such blocking reagents include, for instance, denatured salmon sperm DNA at about 100-200 µg/ml. Organic solvent, such as formamide at a concentration of about 35-50% v/v, may also be used under particular circumstances, such as for  
20 RNA:DNA hybridizations. Useful variations on these wash conditions will be readily apparent to those of ordinary skill in the art. Hybridization, particularly under high stringency conditions, may be suggestive of evolutionary similarity between the nucleotides. Such similarity is strongly indicative of a similar role for the nucleotides and their encoded polypeptides.

The term "hybridization complex" refers to a complex formed between two nucleic acid  
25 sequences by virtue of the formation of hydrogen bonds between complementary bases. A hybridization complex may be formed in solution (e.g.,  $C_0t$  or  $R_0t$  analysis) or formed between one nucleic acid sequence present in solution and another nucleic acid sequence immobilized on a solid support (e.g., paper, membranes, filters, chips, pins or glass slides, or any other appropriate substrate to which cells or their nucleic acids have been fixed).

30 The words "insertion" and "addition" refer to changes in an amino acid or nucleotide sequence resulting in the addition of one or more amino acid residues or nucleotides, respectively.

"Immune response" can refer to conditions associated with inflammation, trauma, immune disorders, or infectious or genetic disease, etc. These conditions can be characterized by expression of various factors, e.g., cytokines, chemokines, and other signaling molecules, which may affect

cellular and systemic defense systems.

The term "microarray" refers to an arrangement of distinct polynucleotides on a substrate.

The terms "element" and "array element" in a microarray context, refer to hybridizable polynucleotides arranged on the surface of a substrate.

5 The term "modulate" refers to a change in the activity of MTRP. For example, modulation may cause an increase or a decrease in protein activity, binding characteristics, or any other biological, functional, or immunological properties of MTRP.

The phrases "nucleic acid" and "nucleic acid sequence" refer to a nucleotide, oligonucleotide, polynucleotide, or any fragment thereof. These phrases also refer to DNA or RNA of genomic or  
10 synthetic origin which may be single-stranded or double-stranded and may represent the sense or the antisense strand, to peptide nucleic acid (PNA), or to any DNA-like or RNA-like material.

"Operably linked" refers to the situation in which a first nucleic acid sequence is placed in a functional relationship with the second nucleic acid sequence. For instance, a promoter is operably linked to a coding sequence if the promoter affects the transcription or expression of the coding  
15 sequence. Generally, operably linked DNA sequences may be in close proximity or contiguous and, where necessary to join two protein coding regions, in the same reading frame.

"Peptide nucleic acid" (PNA) refers to an antisense molecule or anti-gene agent which comprises an oligonucleotide of at least about 5 nucleotides in length linked to a peptide backbone of amino acid residues ending in lysine. The terminal lysine confers solubility to the composition.  
20 PNAs preferentially bind complementary single stranded DNA or RNA and stop transcript elongation, and may be pegylated to extend their lifespan in the cell.

"Probe" refers to nucleic acid sequences encoding MTRP, their complements, or fragments thereof, which are used to detect identical, allelic or related nucleic acid sequences. Probes are isolated oligonucleotides or polynucleotides attached to a detectable label or reporter molecule.

25 Typical labels include radioactive isotopes, ligands, chemiluminescent agents, and enzymes.

"Primers" are short nucleic acids, usually DNA oligonucleotides, which may be annealed to a target polynucleotide by complementary base-pairing. The primer may then be extended along the target DNA strand by a DNA polymerase enzyme. Primer pairs can be used for amplification (and identification) of a nucleic acid sequence, e.g., by the polymerase chain reaction (PCR).

30 Probes and primers as used in the present invention typically comprise at least 15 contiguous nucleotides of a known sequence. In order to enhance specificity, longer probes and primers may also be employed, such as probes and primers that comprise at least 20, 25, 30, 40, 50, 60, 70, 80, 90, 100, or at least 150 consecutive nucleotides of the disclosed nucleic acid sequences. Probes and primers may be considerably longer than these examples, and it is understood that any length supported by the

specification, including the tables, figures, and Sequence Listing, may be used.

Methods for preparing and using probes and primers are described in the References, for example Sambrook et al., 1989, Molecular Cloning: A Laboratory Manual, 2<sup>nd</sup> ed., vol. 1-3, Cold Spring Harbor Press, Plainview NY; Ausubel et al., 1987, Current Protocols in Molecular Biology, Greene Publ. Assoc. & Wiley-Intersciences, New York NY; Innis et al., 1990, PCR Protocols, A Guide to Methods and Applications, Academic Press, San Diego CA. PCR primer pairs can be derived from a known sequence, for example, by using computer programs intended for that purpose such as Primer (Version 0.5, 1991, Whitehead Institute for Biomedical Research, Cambridge MA).

Oligonucleotides for use as primers are selected using software known in the art for such purpose. For example, OLIGO 4.06 software is useful for the selection of PCR primer pairs of up to 100 nucleotides each, and for the analysis of oligonucleotides and larger polynucleotides of up to 5,000 nucleotides from an input polynucleotide sequence of up to 32 kilobases. Similar primer selection programs have incorporated additional features for expanded capabilities. For example, the PrimOU primer selection program (available to the public from the Genome Center at University of Texas South West Medical Center, Dallas TX) is capable of choosing specific primers from megabase sequences and is thus useful for designing primers on a genome-wide scope. The Primer3 primer selection program (available to the public from the Whitehead Institute/MIT Center for Genome Research, Cambridge MA) allows the user to input a "mispriming library," in which sequences to avoid as primer binding sites are user-specified. Primer3 is useful, in particular, for the selection of oligonucleotides for microarrays. (The source code for the latter two primer selection programs may also be obtained from their respective sources and modified to meet the user's specific needs.) The PrimeGen program (available to the public from the UK Human Genome Mapping Project Resource Centre, Cambridge UK) designs primers based on multiple sequence alignments, thereby allowing selection of primers that hybridize to either the most conserved or least conserved regions of aligned nucleic acid sequences. Hence, this program is useful for identification of both unique and conserved oligonucleotides and polynucleotide fragments. The oligonucleotides and polynucleotide fragments identified by any of the above selection methods are useful in hybridization technologies, for example, as PCR or sequencing primers, microarray elements, or specific probes to identify fully or partially complementary polynucleotides in a sample of nucleic acids. Methods of oligonucleotide selection are not limited to those described above.

A "recombinant nucleic acid" is a sequence that is not naturally occurring or has a sequence that is made by an artificial combination of two or more otherwise separated segments of sequence. This artificial combination is often accomplished by chemical synthesis or, more commonly, by the artificial manipulation of isolated segments of nucleic acids, e.g., by genetic engineering techniques

such as those described in Sambrook, supra. The term recombinant includes nucleic acids that have been altered solely by addition, substitution, or deletion of a portion of the nucleic acid. Frequently, a recombinant nucleic acid may include a nucleic acid sequence operably linked to a promoter sequence. Such a recombinant nucleic acid may be part of a vector that is used, for example, to  
5 transform a cell.

Alternatively, such recombinant nucleic acids may be part of a viral vector, e.g., based on a vaccinia virus, that could be used to vaccinate a mammal wherein the recombinant nucleic acid is expressed, inducing a protective immunological response in the mammal.

The term "sample" is used in its broadest sense. A sample suspected of containing nucleic  
10 acids encoding MTRP, or fragments thereof, or MTRP itself, may comprise a bodily fluid; an extract from a cell, chromosome, organelle, or membrane isolated from a cell; a cell; genomic DNA, RNA, or cDNA, in solution or bound to a substrate; a tissue; a tissue print; etc.

The terms "specific binding" and "specifically binding" refer to that interaction between a  
15 protein or peptide and an agonist, an antibody, an antagonist, a small molecule, or any natural or synthetic binding composition. The interaction is dependent upon the presence of a particular structure of the protein, e.g., the antigenic determinant or epitope, recognized by the binding molecule. For example, if an antibody is specific for epitope "A," the presence of a polypeptide containing the epitope A, or the presence of free unlabeled A, in a reaction containing free labeled A and the antibody will reduce the amount of labeled A that binds to the antibody.

20 The term "substantially purified" refers to nucleic acid or amino acid sequences that are removed from their natural environment and are isolated or separated, and are at least about 60% free, preferably about 75% free, and most preferably about 90% free from other components with which they are naturally associated.

A "substitution" refers to the replacement of one or more amino acids or nucleotides by  
25 different amino acids or nucleotides, respectively.

"Substrate" refers to any suitable rigid or semi-rigid support including membranes, filters, chips, slides, wafers, fibers, magnetic or nonmagnetic beads, gels, tubing, plates, polymers, microparticles and capillaries. The substrate can have a variety of surface forms, such as wells, trenches, pins, channels and pores, to which polynucleotides or polypeptides are bound.

30 "Transformation" describes a process by which exogenous DNA enters and changes a recipient cell. Transformation may occur under natural or artificial conditions according to various methods well known in the art, and may rely on any known method for the insertion of foreign nucleic acid sequences into a prokaryotic or eukaryotic host cell. The method for transformation is selected based on the type of host cell being transformed and may include, but is not limited to, viral infection,

electroporation, heat shock, lipofection, and particle bombardment. The term "transformed" cells includes stably transformed cells in which the inserted DNA is capable of replication either as an autonomously replicating plasmid or as part of the host chromosome, as well as transiently transformed cells which express the inserted DNA or RNA for limited periods of time.

5 A "variant" of a particular nucleic acid sequence is defined as a nucleic acid sequence having at least 40% sequence identity to the particular nucleic acid sequence over a certain length of one of the nucleic acid sequences using blastn with the "BLAST 2 Sequences" tool Version 2.0.9 (May-07-1999) set at default parameters. Such a pair of nucleic acids may show, for example, at least 50%, at least 60%, at least 70%, at least 80%, at least 85%, at least 90%, at least 95% or at least 98% or  
10 greater sequence identity over a certain defined length. A variant may be described as, for example, an "allelic" (as defined above), "splice," "species," or "polymorphic" variant. A splice variant may have significant identity to a reference molecule, but will generally have a greater or lesser number of polynucleotides due to alternate splicing of exons during mRNA processing. The corresponding polypeptide may possess additional functional domains or lack domains that are present in the  
15 reference molecule. Species variants are polynucleotide sequences that vary from one species to another. The resulting polypeptides generally will have significant amino acid identity relative to each other. A polymorphic variant is a variation in the polynucleotide sequence of a particular gene between individuals of a given species. Polymorphic variants also may encompass "single nucleotide polymorphisms" (SNPs) in which the polynucleotide sequence varies by one nucleotide base. The  
20 presence of SNPs may be indicative of, for example, a certain population, a disease state, or a propensity for a disease state.

A "variant" of a particular polypeptide sequence is defined as a polypeptide sequence having at least 40% sequence identity to the particular polypeptide sequence over a certain length of one of the polypeptide sequences using blastp with the "BLAST 2 Sequences" tool Version 2.0.9 (May-07-  
25 1999) set at default parameters. Such a pair of polypeptides may show, for example, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, or at least 98% or greater sequence identity over a certain defined length of one of the polypeptides.

## THE INVENTION

The invention is based on the discovery of new human membrane transport proteins (MTRP),  
30 the polynucleotides encoding MTRP, and the use of these compositions for the diagnosis, treatment, or prevention of membrane transport disorders; immune/inflammatory disorders; and cell proliferative disorders including cancer.

Table 1 lists the Incyte clones used to assemble full length nucleotide sequences encoding MTRP. Columns 1 and 2 show the sequence identification numbers (SEQ ID NOs) of the polypeptide

and nucleotide sequences, respectively. Column 3 shows the clone IDs of the Incyte clones in which nucleic acids encoding each MTRP were identified, and column 4 shows the cDNA libraries from which these clones were isolated. Column 5 shows Incyte clones and their corresponding cDNA libraries. Clones for which cDNA libraries are not indicated were derived from pooled cDNA libraries. The Incyte clones in column 5 were used to assemble the consensus nucleotide sequence of each MTRP and are useful as fragments in hybridization technologies.

The columns of Table 2 show various properties of each of the polypeptides of the invention: column 1 references the SEQ ID NO; column 2 shows the number of amino acid residues in each polypeptide; column 3 shows potential phosphorylation sites; column 4 shows potential glycosylation sites; column 5 shows the amino acid residues comprising signature sequences and motifs; column 6 shows homologous sequences as identified by BLAST analysis; and column 7 shows analytical methods and in some cases, searchable databases to which the analytical methods were applied. The methods of column 7 were used to characterize each polypeptide through sequence homology and protein motifs.

As shown in Figures 1A, 1B, 1C, and 1D, MTRP-3 has chemical and structural similarity with mouse fatty acid transport protein (FATP; GI 2612939; SEQ ID NO:35). In particular, MTRP-3 and FATP share 65% identity. As shown in Figures 2A, 2B, 2C, and 2D, MTRP-4 has chemical and structural similarity with Schistosoma mansoni ATP-binding cassette family protein, SMDR-1 (GI 425474; SEQ ID NO:36). In particular, MTRP-4 and SMDR-1 share 38% identity. As shown in Figures 3A, 3B, 3C, and 3D, MTRP-5 has chemical and structural similarity with rat sodium-dependent multivitamin transporter (SMVT; GI 3015617; SEQ ID NO:37). In particular, MTRP-5 and SMVT share 82% identity.

The columns of Table 3 show the tissue-specificity and diseases, disorders, or conditions associated with nucleotide sequences encoding MTRP. The first column of Table 3 lists the nucleotide SEQ ID NOs. Column 2 lists tissue categories which express MTRP as a fraction of total tissues expressing MTRP. Column 3 lists diseases, disorders, or conditions associated with those tissues expressing MTRP as a fraction of total tissues expressing MTRP. Column 4 lists the vectors used to subclone each cDNA library.

Of particular note are the expression patterns of SEQ ID NO:30 and SEQ ID NO:31. SEQ ID NO:30 is expressed in only five libraries, of which at least four (80%) are associated with cell proliferation and at least one (20%) with inflammation. Two (40%) of the five libraries are associated with cardiovascular tissue, and one each (20%) with gastrointestinal, nervous, and reproductive tissues. SEQ ID NO:31 is expressed in only four libraries, of which at least three (75%) are associated with cell proliferation and at least two (50%) with inflammation or the immune response.

Two (50%) of the four libraries are associated with hematopoietic/immune tissue, and one each (25%) with cardiovascular and reproductive tissues.

The following fragments of the nucleotide sequences encoding MTRP are useful, for example, in hybridization or amplification technologies to identify SEQ ID NO:18-34 and to distinguish between SEQ ID NO:18-34 and related polynucleotide sequences. The useful fragments include the fragment of SEQ ID NO:18 from about nucleotide 110 to about nucleotide 154; the fragment of SEQ ID NO:19 from about nucleotide 759 to about nucleotide 839; the fragment of SEQ ID NO:20 from about nucleotide 1531 to about nucleotide 1578; the fragment of SEQ ID NO:21 from about nucleotide 538 to about nucleotide 597; the fragment of SEQ ID NO:22 from about nucleotide 2241 to about nucleotide 2294; the fragment of SEQ ID NO:23 from about nucleotide 116 to about nucleotide 145; the fragment of SEQ ID NO:24 from about nucleotide 60 to about nucleotide 89; the fragment of SEQ ID NO:25 from about nucleotide 160 to about nucleotide 189; the fragment of SEQ ID NO:26 from about nucleotide 763 to about nucleotide 792; the fragment of SEQ ID NO:27 from about nucleotide 43 to about nucleotide 72; the fragment of SEQ ID NO:28 from about nucleotide 361 to about nucleotide 405; the fragment of SEQ ID NO:29 from about nucleotide 35 to about nucleotide 79; the fragment of SEQ ID NO:30 from about nucleotide 206 to about nucleotide 250; the fragment of SEQ ID NO:31 from about nucleotide 71 to about nucleotide 115; the fragment of SEQ ID NO:32 from about nucleotide 161 to about nucleotide 205; the fragment of SEQ ID NO:33 from about nucleotide 364 to about nucleotide 408; and the fragment of SEQ ID NO:34 from about nucleotide 18 to about nucleotide 62. The polypeptides encoded by the specified fragments of SEQ ID NO:20-30 and SEQ ID NO:32-34 are useful, for example, as immunogenic peptides.

The columns of Table 4 show descriptions of the tissues used to construct the cDNA libraries from which cDNA clones encoding MTRP were isolated. Column 1 references the nucleotide SEQ ID NOs, column 2 shows the cDNA libraries from which these clones were isolated, and column 3 shows the tissue origins and other descriptive information relevant to the cDNA libraries in column 2.

The invention also encompasses MTRP variants. A preferred MTRP variant is one which has at least about 80%, or alternatively at least about 90%, or even at least about 95% amino acid sequence identity to the MTRP amino acid sequence, and which contains at least one functional or structural characteristic of MTRP.

The invention also encompasses polynucleotides which encode MTRP. In a particular embodiment, the invention encompasses a polynucleotide sequence comprising a sequence selected from the group consisting of SEQ ID NO:18-34, which encodes MTRP.

The invention also encompasses a variant of a polynucleotide sequence encoding MTRP. In particular, such a variant polynucleotide sequence will have at least about 75%, or alternatively at



least about 85%, or even at least about 95% polynucleotide sequence identity to the polynucleotide sequence encoding MTRP. A particular aspect of the invention encompasses a variant of a polynucleotide sequence comprising a sequence selected from the group consisting of SEQ ID NO:18-34 which has at least about 75%, or alternatively at least about 85%, or even at least about 5 95% polynucleotide sequence identity to a nucleic acid sequence selected from the group consisting of SEQ ID NO:18-34. Any one of the polynucleotide variants described above can encode an amino acid sequence which contains at least one functional or structural characteristic of MTRP.

It will be appreciated by those skilled in the art that as a result of the degeneracy of the genetic code, a multitude of polynucleotide sequences encoding MTRP, some bearing minimal 10 similarity to the polynucleotide sequences of any known and naturally occurring gene, may be produced. Thus, the invention contemplates each and every possible variation of polynucleotide sequence that could be made by selecting combinations based on possible codon choices. These combinations are made in accordance with the standard triplet genetic code as applied to the polynucleotide sequence of naturally occurring MTRP, and all such variations are to be considered as 15 being specifically disclosed.

Although nucleotide sequences which encode MTRP and its variants are generally capable of hybridizing to the nucleotide sequence of the naturally occurring MTRP under appropriately selected conditions of stringency, it may be advantageous to produce nucleotide sequences encoding MTRP or its derivatives possessing a substantially different codon usage, e.g., inclusion of non-naturally 20 occurring codons. Codons may be selected to increase the rate at which expression of the peptide occurs in a particular prokaryotic or eukaryotic host in accordance with the frequency with which particular codons are utilized by the host. Other reasons for substantially altering the nucleotide sequence encoding MTRP and its derivatives without altering the encoded amino acid sequences include the production of RNA transcripts having more desirable properties, such as a greater 25 half-life, than transcripts produced from the naturally occurring sequence.

The invention also encompasses production of DNA sequences which encode MTRP and MTRP derivatives, or fragments thereof, entirely by synthetic chemistry. After production, the synthetic sequence may be inserted into any of the many available expression vectors and cell systems using reagents well known in the art. Moreover, synthetic chemistry may be used to introduce 30 mutations into a sequence encoding MTRP or any fragment thereof.

Also encompassed by the invention are polynucleotide sequences that are capable of hybridizing to the claimed polynucleotide sequences, and, in particular, to those shown in SEQ ID NO:18-34 and fragments thereof under various conditions of stringency. (See, e.g., Wahl, G.M. and S.L. Berger (1987) *Methods Enzymol.* 152:399-407; Kimmel, A.R. (1987) *Methods Enzymol.*

152:507-511.) Hybridization conditions, including annealing and wash conditions, are described in "Definitions."

Methods for DNA sequencing are well known in the art and may be used to practice any of the embodiments of the invention. The methods may employ such enzymes as the Klenow fragment of DNA polymerase I, SEQUENASE (US Biochemical, Cleveland OH), Taq polymerase (Perkin-Elmer), thermostable T7 polymerase (Amersham Pharmacia Biotech, Piscataway NJ), or combinations of polymerases and proofreading exonucleases such as those found in the ELONGASE amplification system (Life Technologies, Gaithersburg MD). Preferably, sequence preparation is automated with machines such as the MICROLAB 2200 liquid transfer system (Hamilton, Reno NV), PTC200 thermal cycler (MJ Research, Watertown MA) and ABI CATALYST 800 thermal cycler (Perkin-Elmer). Sequencing is then carried out using either the ABI 373 or 377 DNA sequencing system (Perkin-Elmer), the MEGABACE 1000 DNA sequencing system (Molecular Dynamics, Sunnyvale CA), or other systems known in the art. The resulting sequences are analyzed using a variety of algorithms which are well known in the art. (See, e.g., Ausubel, F.M. (1997) Short Protocols in Molecular Biology, John Wiley & Sons, New York NY, unit 7.7; Meyers, R.A. (1995) Molecular Biology and Biotechnology, Wiley VCH, New York NY, pp. 856-853.)

The nucleic acid sequences encoding MTRP may be extended utilizing a partial nucleotide sequence and employing various PCR-based methods known in the art to detect upstream sequences, such as promoters and regulatory elements. For example, one method which may be employed, restriction-site PCR, uses universal and nested primers to amplify unknown sequence from genomic DNA within a cloning vector. (See, e.g., Sarkar, G. (1993) PCR Methods Applic. 2:318-322.) Another method, inverse PCR, uses primers that extend in divergent directions to amplify unknown sequence from a circularized template. The template is derived from restriction fragments comprising a known genomic locus and surrounding sequences. (See, e.g., Triglia, T. et al. (1988) Nucleic Acids Res. 16:8186.) A third method, capture PCR, involves PCR amplification of DNA fragments adjacent to known sequences in human and yeast artificial chromosome DNA. (See, e.g., Lagerstrom, M. et al. (1991) PCR Methods Applic. 1:111-119.) In this method, multiple restriction enzyme digestions and ligations may be used to insert an engineered double-stranded sequence into a region of unknown sequence before performing PCR. Other methods which may be used to retrieve unknown sequences are known in the art. (See, e.g., Parker, J.D. et al. (1991) Nucleic Acids Res. 19:3055-3060). Additionally, one may use PCR, nested primers, and PROMOTERFINDER libraries (Clontech, Palo Alto CA) to walk genomic DNA. This procedure avoids the need to screen libraries and is useful in finding intron/exon junctions. For all PCR-based methods, primers may be designed using commercially available software, such as OLIGO 4.06 Primer Analysis software (National

Biosciences, Plymouth MN) or another appropriate program, to be about 22 to 30 nucleotides in length, to have a GC content of about 50% or more, and to anneal to the template at temperatures of about 68°C to 72°C.

When screening for full-length cDNAs, it is preferable to use libraries that have been size-selected to include larger cDNAs. In addition, random-primed libraries, which often include sequences containing the 5' regions of genes, are preferable for situations in which an oligo d(T) library does not yield a full-length cDNA. Genomic libraries may be useful for extension of sequence into 5' non-transcribed regulatory regions.

Capillary electrophoresis systems which are commercially available may be used to analyze the size or confirm the nucleotide sequence of sequencing or PCR products. In particular, capillary sequencing may employ flowable polymers for electrophoretic separation, four different nucleotide-specific, laser-stimulated fluorescent dyes, and a charge coupled device camera for detection of the emitted wavelengths. Output/light intensity may be converted to electrical signal using appropriate software (e.g., GENOTYPER and SEQUENCE NAVIGATOR, Perkin-Elmer), and the entire process from loading of samples to computer analysis and electronic data display may be computer controlled. Capillary electrophoresis is especially preferable for sequencing small DNA fragments which may be present in limited amounts in a particular sample.

In another embodiment of the invention, polynucleotide sequences or fragments thereof which encode MTRP may be cloned in recombinant DNA molecules that direct expression of MTRP, or fragments or functional equivalents thereof, in appropriate host cells. Due to the inherent degeneracy of the genetic code, other DNA sequences which encode substantially the same or a functionally equivalent amino acid sequence may be produced and used to express MTRP.

The nucleotide sequences of the present invention can be engineered using methods generally known in the art in order to alter MTRP-encoding sequences for a variety of purposes including, but not limited to, modification of the cloning, processing, and/or expression of the gene product. DNA shuffling by random fragmentation and PCR reassembly of gene fragments and synthetic oligonucleotides may be used to engineer the nucleotide sequences. For example, oligonucleotide-mediated site-directed mutagenesis may be used to introduce mutations that create new restriction sites, alter glycosylation patterns, change codon preference, produce splice variants, and so forth.

In another embodiment, sequences encoding MTRP may be synthesized, in whole or in part, using chemical methods well known in the art. (See, e.g., Caruthers, M.H. et al. (1980) *Nucleic Acids Symp. Ser.* 7:215-223; and Horn, T. et al. (1980) *Nucleic Acids Symp. Ser.* 7:225-232.) Alternatively, MTRP itself or a fragment thereof may be synthesized using chemical methods. For example, peptide synthesis can be performed using various solid-phase techniques. (See, e.g.,

Roberge, J.Y. et al. (1995) Science 269:202-204.) Automated synthesis may be achieved using the ABI 431A peptide synthesizer (Perkin-Elmer). Additionally, the amino acid sequence of MTRP, or any part thereof, may be altered during direct synthesis and/or combined with sequences from other proteins, or any part thereof, to produce a variant polypeptide.

5 The peptide may be substantially purified by preparative high performance liquid chromatography. (See, e.g., Chiez, R.M. and F.Z. Regnier (1990) Methods Enzymol. 182:392-421.) The composition of the synthetic peptides may be confirmed by amino acid analysis or by sequencing. (See, e.g., Creighton, T. (1984) Proteins, Structures and Molecular Properties, WH Freeman, New York NY.)

10 In order to express a biologically active MTRP, the nucleotide sequences encoding MTRP or derivatives thereof may be inserted into an appropriate expression vector, i.e., a vector which contains the necessary elements for transcriptional and translational control of the inserted coding sequence in a suitable host. These elements include regulatory sequences, such as enhancers, constitutive and inducible promoters, and 5' and 3' untranslated regions in the vector and in polynucleotide sequences  
15 encoding MTRP. Such elements may vary in their strength and specificity. Specific initiation signals may also be used to achieve more efficient translation of sequences encoding MTRP. Such signals include the ATG initiation codon and adjacent sequences, e.g. the Kozak sequence. In cases where sequences encoding MTRP and its initiation codon and upstream regulatory sequences are inserted into the appropriate expression vector, no additional transcriptional or translational control signals  
20 may be needed. However, in cases where only coding sequence, or a fragment thereof, is inserted, exogenous translational control signals including an in-frame ATG initiation codon should be provided by the vector. Exogenous translational elements and initiation codons may be of various origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of enhancers appropriate for the particular host cell system used. (See, e.g., Scharf, D. et al. (1994) Results Probl. Cell Differ. 20:125-162.)

25 Methods which are well known to those skilled in the art may be used to construct expression vectors containing sequences encoding MTRP and appropriate transcriptional and translational control elements. These methods include in vitro recombinant DNA techniques, synthetic techniques, and in vivo genetic recombination. (See, e.g., Sambrook, J. et al. (1989) Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Press, Plainview NY, ch. 4, 8, and 16-17; Ausubel, F.M. et al. (1995) Current Protocols in Molecular Biology, John Wiley & Sons, New York NY, ch. 9, 13, and 16.)

A variety of expression vector/host systems may be utilized to contain and express sequences encoding MTRP. These include, but are not limited to, microorganisms such as bacteria transformed

with recombinant bacteriophage, plasmid, or cosmid DNA expression vectors; yeast transformed with yeast expression vectors; insect cell systems infected with viral expression vectors (e.g., baculovirus); plant cell systems transformed with viral expression vectors (e.g., cauliflower mosaic virus, CaMV, or tobacco mosaic virus, TMV) or with bacterial expression vectors (e.g., Ti or pBR322 plasmids); or  
5 animal cell systems. The invention is not limited by the host cell employed.

In bacterial systems, a number of cloning and expression vectors may be selected depending upon the use intended for polynucleotide sequences encoding MTRP. For example, routine cloning, subcloning, and propagation of polynucleotide sequences encoding MTRP can be achieved using a multifunctional *E. coli* vector such as PBLUESCRIPT (Stratagene, La Jolla CA) or PSPORT1  
10 plasmid (Life Technologies). Ligation of sequences encoding MTRP into the vector's multiple cloning site disrupts the *lacZ* gene, allowing a colorimetric screening procedure for identification of transformed bacteria containing recombinant molecules. In addition, these vectors may be useful for *in vitro* transcription, dideoxy sequencing, single strand rescue with helper phage, and creation of nested deletions in the cloned sequence. (See, e.g., Van Heeke, G. and S.M. Schuster (1989) J. Biol.  
15 Chem. 264:5503-5509.) When large quantities of MTRP are needed, e.g. for the production of antibodies, vectors which direct high level expression of MTRP may be used. For example, vectors containing the strong, inducible T5 or T7 bacteriophage promoter may be used.

Yeast expression systems may be used for production of MTRP. A number of vectors containing constitutive or inducible promoters, such as alpha factor, alcohol oxidase, and PGH  
20 promoters, may be used in the yeast *Saccharomyces cerevisiae* or *Pichia pastoris*. In addition, such vectors direct either the secretion or intracellular retention of expressed proteins and enable integration of foreign sequences into the host genome for stable propagation. (See, e.g., Ausubel, 1995, *supra*; Bitter, G.A. et al. (1987) Methods Enzymol. 153:516-544; and Scorer, C.A. et al. (1994) Bio/Technology 12:181-184.)

Plant systems may also be used for expression of MTRP. Transcription of sequences  
25 encoding MTRP may be driven viral promoters, e.g., the 35S and 19S promoters of CaMV used alone or in combination with the omega leader sequence from TMV (Takamatsu, N. (1987) EMBO J. 6:307-311). Alternatively, plant promoters such as the small subunit of RUBISCO or heat shock promoters may be used. (See, e.g., Coruzzi, G. et al. (1984) EMBO J. 3:1671-1680; Broglie, R. et al.  
30 (1984) Science 224:838-843; and Winter, J. et al. (1991) Results Probl. Cell Differ. 17:85-105.) These constructs can be introduced into plant cells by direct DNA transformation or pathogen-mediated transfection. (See, e.g., The McGraw Hill Yearbook of Science and Technology (1992) McGraw Hill, New York NY, pp. 191-196.)

In mammalian cells, a number of viral-based expression systems may be utilized. In cases

where an adenovirus is used as an expression vector, sequences encoding MTRP may be ligated into an adenovirus transcription/translation complex consisting of the late promoter and tripartite leader sequence. Insertion in a non-essential E1 or E3 region of the viral genome may be used to obtain infective virus which expresses MTRP in host cells. (See, e.g., Logan, J. and T. Shenk (1984) Proc. Natl. Acad. Sci. USA 81:3655-3659.) In addition, transcription enhancers, such as the Rous sarcoma virus (RSV) enhancer, may be used to increase expression in mammalian host cells. SV40 or EBV-based vectors may also be used for high-level protein expression.

Human artificial chromosomes (HACs) may also be employed to deliver larger fragments of DNA than can be contained in and expressed from a plasmid. HACs of about 6 kb to 10 Mb are constructed and delivered via conventional delivery methods (liposomes, polycationic amino polymers, or vesicles) for therapeutic purposes. (See, e.g., Harrington, J.J. et al. (1997) Nat. Genet. 15:345-355.)

For long term production of recombinant proteins in mammalian systems, stable expression of MTRP in cell lines is preferred. For example, sequences encoding MTRP can be transformed into cell lines using expression vectors which may contain viral origins of replication and/or endogenous expression elements and a selectable marker gene on the same or on a separate vector. Following the introduction of the vector, cells may be allowed to grow for about 1 to 2 days in enriched media before being switched to selective media. The purpose of the selectable marker is to confer resistance to a selective agent, and its presence allows growth and recovery of cells which successfully express the introduced sequences. Resistant clones of stably transformed cells may be propagated using tissue culture techniques appropriate to the cell type.

Any number of selection systems may be used to recover transformed cell lines. These include, but are not limited to, the herpes simplex virus thymidine kinase and adenine phosphoribosyltransferase genes, for use in *tk* and *ap<sup>r</sup>* cells, respectively. (See, e.g., Wigler, M. et al. (1977) Cell 11:223-232; Lowy, I. et al. (1980) Cell 22:817-823.) Also, antimetabolite, antibiotic, or herbicide resistance can be used as the basis for selection. For example, *dhfr* confers resistance to methotrexate; *neo* confers resistance to the aminoglycosides neomycin and G-418; and *als* and *pat* confer resistance to chlorsulfuron and phosphinotricin acetyltransferase, respectively. (See, e.g., Wigler, M. et al. (1980) Proc. Natl. Acad. Sci. USA 77:3567-3570; Colbere-Garapin, F. et al. (1981) J. Mol. Biol. 150:1-14.) Additional selectable genes have been described, e.g., *trpB* and *hisD*, which alter cellular requirements for metabolites. (See, e.g., Hartman, S.C. and R.C. Mulligan (1988) Proc. Natl. Acad. Sci. USA 85:8047-8051.) Visible markers, e.g., anthocyanins, green fluorescent proteins (GFP; Clontech),  $\beta$  glucuronidase and its substrate  $\beta$ -glucuronide, or luciferase and its substrate luciferin may be used. These markers can be used not only to identify transformants, but also to

quantify the amount of transient or stable protein expression attributable to a specific vector system. (See, e.g., Rhodes, C.A. (1995) *Methods Mol. Biol.* 55:121-131.)

Although the presence/absence of marker gene expression suggests that the gene of interest is also present, the presence and expression of the gene may need to be confirmed. For example, if the sequence encoding MTRP is inserted within a marker gene sequence, transformed cells containing sequences encoding MTRP can be identified by the absence of marker gene function. Alternatively, a marker gene can be placed in tandem with a sequence encoding MTRP under the control of a single promoter. Expression of the marker gene in response to induction or selection usually indicates expression of the tandem gene as well.

In general, host cells that contain the nucleic acid sequence encoding MTRP and that express MTRP may be identified by a variety of procedures known to those of skill in the art. These procedures include, but are not limited to, DNA-DNA or DNA-RNA hybridizations, PCR amplification, and protein bioassay or immunoassay techniques which include membrane, solution, or chip based technologies for the detection and/or quantification of nucleic acid or protein sequences.

Immunological methods for detecting and measuring the expression of MTRP using either specific polyclonal or monoclonal antibodies are known in the art. Examples of such techniques include enzyme-linked immunosorbent assays (ELISAs), radioimmunoassays (RIAs), and fluorescence activated cell sorting (FACS). A two-site, monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two non-interfering epitopes on MTRP is preferred, but a competitive binding assay may be employed. These and other assays are well known in the art. (See, e.g., Hampton, R. et al. (1990) *Serological Methods, a Laboratory Manual*, APS Press, St. Paul MN, Sect. IV; Coligan, J.E. et al. (1997) *Current Protocols in Immunology*, Greene Pub. Associates and Wiley-Interscience, New York NY; and Pound, J.D. (1998) *Immunochemical Protocols*, Humana Press, Totowa NJ.)

A wide variety of labels and conjugation techniques are known by those skilled in the art and may be used in various nucleic acid and amino acid assays. Means for producing labeled hybridization or PCR probes for detecting sequences related to polynucleotides encoding MTRP include oligolabeling, nick translation, end-labeling, or PCR amplification using a labeled nucleotide. Alternatively, the sequences encoding MTRP, or any fragments thereof, may be cloned into a vector for the production of an mRNA probe. Such vectors are known in the art, are commercially available, and may be used to synthesize RNA probes *in vitro* by addition of an appropriate RNA polymerase such as T7, T3, or SP6 and labeled nucleotides. These procedures may be conducted using a variety of commercially available kits, such as those provided by Amersham Pharmacia Biotech, Promega (Madison WI), and US Biochemical. Suitable reporter molecules or labels which may be used for

ease of detection include radionuclides, enzymes, fluorescent, chemiluminescent, or chromogenic agents, as well as substrates, cofactors, inhibitors, magnetic particles, and the like.

Host cells transformed with nucleotide sequences encoding MTRP may be cultured under conditions suitable for the expression and recovery of the protein from cell culture. The protein  
5 produced by a transformed cell may be secreted or retained intracellularly depending on the sequence and/or the vector used. As will be understood by those of skill in the art, expression vectors containing polynucleotides which encode MTRP may be designed to contain signal sequences which direct secretion of MTRP through a prokaryotic or eukaryotic cell membrane.

In addition, a host cell strain may be chosen for its ability to modulate expression of the  
10 inserted sequences or to process the expressed protein in the desired fashion. Such modifications of the polypeptide include, but are not limited to, acetylation, carboxylation, glycosylation, phosphorylation, lipidation, and acylation. Post-translational processing which cleaves a "prepro" or "pro" form of the protein may also be used to specify protein targeting, folding, and/or activity. Different host cells which have specific cellular machinery and characteristic mechanisms for  
15 post-translational activities (e.g., CHO, HeLa, MDCK, HEK293, and WI38) are available from the American Type Culture Collection (ATCC, Manassas VA) and may be chosen to ensure the correct modification and processing of the foreign protein.

In another embodiment of the invention, natural, modified, or recombinant nucleic acid sequences encoding MTRP may be ligated to a heterologous sequence resulting in translation of a  
20 fusion protein in any of the aforementioned host systems. For example, a chimeric MTRP protein containing a heterologous moiety that can be recognized by a commercially available antibody may facilitate the screening of peptide libraries for inhibitors of MTRP activity. Heterologous protein and peptide moieties may also facilitate purification of fusion proteins using commercially available affinity matrices. Such moieties include, but are not limited to, glutathione S-transferase (GST),  
25 maltose binding protein (MBP), thioredoxin (Trx), calmodulin binding peptide (CBP), 6-His, FLAG, *c-myc*, and hemagglutinin (HA). GST, MBP, Trx, CBP, and 6-His enable purification of their cognate fusion proteins on immobilized glutathione, maltose, phenylarsine oxide, calmodulin, and metal-chelate resins, respectively. FLAG, *c-myc*, and hemagglutinin (HA) enable immunoaffinity  
30 purification of fusion proteins using commercially available monoclonal and polyclonal antibodies that specifically recognize these epitope tags. A fusion protein may also be engineered to contain a proteolytic cleavage site located between the MTRP encoding sequence and the heterologous protein sequence, so that MTRP may be cleaved away from the heterologous moiety following purification. Methods for fusion protein expression and purification are discussed in Ausubel (1995, supra, ch. 10). A variety of commercially available kits may also be used to facilitate expression and purification of



fusion proteins.

In a further embodiment of the invention, synthesis of radiolabeled MTRP may be achieved in vitro using the TNT rabbit reticulocyte lysate or wheat germ extract system (Promega). These systems couple transcription and translation of protein-coding sequences operably associated with the T7, T3, or SP6 promoters. Translation takes place in the presence of a radiolabeled amino acid precursor, for example, <sup>35</sup>S-methionine.

Fragments of MTRP may be produced not only by recombinant means, but also by direct peptide synthesis using solid-phase techniques. (See, e.g., Creighton, supra, pp. 55-60.) Protein synthesis may be performed by manual techniques or by automation. Automated synthesis may be achieved, for example, using the ABI 431A peptide synthesizer (Perkin-Elmer). Various fragments of MTRP may be synthesized separately and then combined to produce the full length molecule.

### THERAPEUTICS

Chemical and structural similarity, e.g., in the context of sequences and motifs, exists between regions of MTRP and membrane transport proteins, including amino acid transporters, ABC transporters, nucleotide-sugar transporters, transmembrane carrier proteins, and ATP-dependent transporter proteins. In addition, the expression of MTRP is closely associated with nervous, reproductive, and gastrointestinal tissues; cancer and other cell proliferative conditions; and with inflammation and the immune response. Therefore, MTRP appears to play a role in membrane transport disorders; immune/inflammatory disorders; and cell proliferative disorders including cancer. In the treatment of disorders associated with increased MTRP expression or activity, it is desirable to decrease the expression or activity of MTRP. In the treatment of disorders associated with decreased MTRP expression or activity, it is desirable to increase the expression or activity of MTRP.

Therefore, in one embodiment, MTRP or a fragment or derivative thereof may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of MTRP. Examples of such disorders include, but are not limited to, a membrane transport disorder such as cystinuria, dibasicaminoaciduria, hypercystinuria, lysinuria, hartnup disease, tryptophan malabsorption, methionine malabsorption, histidinuria, iminoglycinuria, dicarboxylicaminoaciduria, cystinosis, renal glycosuria, glucose-galactose malabsorption, familial hypercholesterolemia, hypouricemia, familial hypophosphatemic rickets, congenital chloridorrhea, cystic fibrosis, familial goiter, distal renal tubular acidosis, Menkes' disease, lethal diarrhea, nephrogenic diabetes insipidus, juvenile pernicious anemia, folate malabsorption, adrenoleukodystrophy, hereditary myoglobinuria, Zellweger syndrome, hyperinsulinemic hypoglycemia, akinesia, amyotrophic lateral sclerosis, ataxia telangiectasia, cystic fibrosis, Becker's muscular dystrophy, Bell's palsy, Charcot-Marie Tooth disease, diabetes mellitus, diabetes insipidus,

diabetic neuropathy, Duchenne muscular dystrophy, hyperkalemic periodic paralysis, normokalemic periodic paralysis, Parkinson's disease, malignant hyperthermia, multidrug resistance, myasthenia gravis, myotonic dystrophy, catatonia, tardive dyskinesia, dystonias, peripheral neuropathy, cerebral neoplasms, and prostate cancer; a cardiac disorder associated with transport such as angina, bradyarrhythmia, tachyarrhythmia, hypertension, Long QT syndrome, myocarditis, cardiomyopathy, nemaline myopathy, centronuclear myopathy, lipid myopathy, mitochondrial myopathy, thyrotoxic myopathy, ethanol myopathy, dermatomyositis, inclusion body myositis, infectious myositis, and polymyositis; a neurological disorder associated with transport such as Alzheimer's disease, amnesia, bipolar disorder, dementia, depression, epilepsy, Tourette's disorder, paranoid psychoses, and schizophrenia; and an other disorder associated with transport such as neurofibromatosis, postherpetic neuralgia, trigeminal neuropathy, sarcoidosis, sickle cell anemia, Wilson's disease, cataracts, infertility, pulmonary artery stenosis, sensorineural autosomal deafness, hyperglycemia, hypoglycemia, Grave's disease, goiter, Cushing's disease, Addison's disease, glucose-galactose malabsorption syndrome, and hypercholesterolemia; an immune/inflammatory disorder such as acquired immunodeficiency syndrome (AIDS), Addison's disease, adult respiratory distress syndrome, allergies, ankylosing spondylitis, amyloidosis, anemia, asthma, atherosclerosis, autoimmune hemolytic anemia, autoimmune thyroiditis, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), bronchitis, cholecystitis, contact dermatitis, Crohn's disease, atopic dermatitis, dermatomyositis, diabetes mellitus, emphysema, episodic lymphopenia with lymphocytotoxins, erythroblastosis fetalis, erythema nodosum, atrophic gastritis, glomerulonephritis, Goodpasture's syndrome, gout, Graves' disease, Hashimoto's thyroiditis, hypereosinophilia, irritable bowel syndrome, multiple sclerosis, myasthenia gravis, myocardial or pericardial inflammation, osteoarthritis, osteoporosis, pancreatitis, polymyositis, psoriasis, Reiter's syndrome, rheumatoid arthritis, scleroderma, Sjögren's syndrome, systemic anaphylaxis, systemic lupus erythematosus, systemic sclerosis, thrombocytopenic purpura, ulcerative colitis, uveitis, Werner syndrome, complications of cancer, hemodialysis, and extracorporeal circulation; a viral, bacterial, fungal, parasitic, protozoal, or helminthic infection; and trauma; a cell proliferative disorder such as actinic keratosis, arteriosclerosis, atherosclerosis, bursitis, cirrhosis, hepatitis, mixed connective tissue disease (MCTD), myelofibrosis, paroxysmal nocturnal hemoglobinuria, polycythemia vera, psoriasis, primary thrombocythemia; and a cancer including adenocarcinoma, leukemia, lymphoma, melanoma, myeloma, sarcoma, teratocarcinoma; and, in particular, a cancer of the adrenal gland, bladder, bone, bone marrow, brain, breast, cervix, gall bladder, ganglia, gastrointestinal tract, heart, kidney, liver, lung, muscle, ovary, pancreas, parathyroid, penis, prostate, salivary glands, skin, spleen, testis, thymus, thyroid, and uterus.

In another embodiment, a vector capable of expressing MTRP or a fragment or derivative thereof may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of MTRP including, but not limited to, those described above.

In a further embodiment, a pharmaceutical composition comprising a substantially purified MTRP in conjunction with a suitable pharmaceutical carrier may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of MTRP including, but not limited to, those provided above.

In still another embodiment, an agonist which modulates the activity of MTRP may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of MTRP including, but not limited to, those listed above.

In a further embodiment, an antagonist of MTRP may be administered to a subject to treat or prevent a disorder associated with increased expression or activity of MTRP. Examples of such disorders include, but are not limited to, those membrane transport disorders; immune/inflammatory disorders; and cell proliferative disorders including cancer described above. In one aspect, an antibody which specifically binds MTRP may be used directly as an antagonist or indirectly as a targeting or delivery mechanism for bringing a pharmaceutical agent to cells or tissues which express MTRP.

In an additional embodiment, a vector expressing the complement of the polynucleotide encoding MTRP may be administered to a subject to treat or prevent a disorder associated with increased expression or activity of MTRP including, but not limited to, those described above.

In other embodiments, any of the proteins, antagonists, antibodies, agonists, complementary sequences, or vectors of the invention may be administered in combination with other appropriate therapeutic agents. Selection of the appropriate agents for use in combination therapy may be made by one of ordinary skill in the art, according to conventional pharmaceutical principles. The combination of therapeutic agents may act synergistically to effect the treatment or prevention of the various disorders described above. Using this approach, one may be able to achieve therapeutic efficacy with lower dosages of each agent, thus reducing the potential for adverse side effects.

An antagonist of MTRP may be produced using methods which are generally known in the art. In particular, purified MTRP may be used to produce antibodies or to screen libraries of pharmaceutical agents to identify those which specifically bind MTRP. Antibodies to MTRP may also be generated using methods that are well known in the art. Such antibodies may include, but are not limited to, polyclonal, monoclonal, chimeric, and single chain antibodies, Fab fragments, and fragments produced by a Fab expression library. Neutralizing antibodies (i.e., those which inhibit dimer formation) are generally preferred for therapeutic use.

For the production of antibodies, various hosts including goats, rabbits, rats, mice, humans, and others may be immunized by injection with MTRP or with any fragment or oligopeptide thereof which has immunogenic properties. Depending on the host species, various adjuvants may be used to increase immunological response. Such adjuvants include, but are not limited to, Freund's, mineral  
5 gels such as aluminum hydroxide, and surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, KLH, and dinitrophenol. Among adjuvants used in humans, BCG (bacilli Calmette-Guerin) and Corynebacterium parvum are especially preferable.

It is preferred that the oligopeptides, peptides, or fragments used to induce antibodies to MTRP have an amino acid sequence consisting of at least about 5 amino acids, and generally will  
10 consist of at least about 10 amino acids. It is also preferable that these oligopeptides, peptides, or fragments are identical to a portion of the amino acid sequence of the natural protein and contain the entire amino acid sequence of a small, naturally occurring molecule. Short stretches of MTRP amino acids may be fused with those of another protein, such as KLH, and antibodies to the chimeric molecule may be produced.

15 Monoclonal antibodies to MTRP may be prepared using any technique which provides for the production of antibody molecules by continuous cell lines in culture. These include, but are not limited to, the hybridoma technique, the human B-cell hybridoma technique, and the EBV-hybridoma technique. (See, e.g., Kohler, G. et al. (1975) Nature 256:495-497; Kozbor, D. et al. (1985) J. Immunol. Methods 81:31-42; Cote, R.J. et al. (1983) Proc. Natl. Acad. Sci. USA 80:2026-2030; and  
20 Cole, S.P. et al. (1984) Mol. Cell Biol. 62:109-120.)

In addition, techniques developed for the production of "chimeric antibodies," such as the splicing of mouse antibody genes to human antibody genes to obtain a molecule with appropriate antigen specificity and biological activity, can be used. (See, e.g., Morrison, S.L. et al. (1984) Proc. Natl. Acad. Sci. USA 81:6851-6855; Neuberger, M.S. et al. (1984) Nature 312:604-608; and Takeda,  
25 S. et al. (1985) Nature 314:452-454.) Alternatively, techniques described for the production of single chain antibodies may be adapted, using methods known in the art, to produce MTRP-specific single chain antibodies. Antibodies with related specificity, but of distinct idiotypic composition, may be generated by chain shuffling from random combinatorial immunoglobulin libraries. (See, e.g., Burton, D.R. (1991) Proc. Natl. Acad. Sci. USA 88:10134-10137.)

30 Antibodies may also be produced by inducing in vivo production in the lymphocyte population or by screening immunoglobulin libraries or panels of highly specific binding reagents as disclosed in the literature. (See, e.g., Orlandi, R. et al. (1989) Proc. Natl. Acad. Sci. USA 86:3833-3837; Winter, G. et al. (1991) Nature 349:293-299.)

Antibody fragments which contain specific binding sites for MTRP may also be generated.

For example, such fragments include, but are not limited to,  $F(ab')_2$  fragments produced by pepsin digestion of the antibody molecule and Fab fragments generated by reducing the disulfide bridges of the  $F(ab')_2$  fragments. Alternatively, Fab expression libraries may be constructed to allow rapid and easy identification of monoclonal Fab fragments with the desired specificity. (See, e.g., Huse, W.D.

5 et al. (1989) Science 246:1275-1281.)

Various immunoassays may be used for screening to identify antibodies having the desired specificity. Numerous protocols for competitive binding or immunoradiometric assays using either polyclonal or monoclonal antibodies with established specificities are well known in the art. Such immunoassays typically involve the measurement of complex formation between MTRP and its  
10 specific antibody. A two-site, monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two non-interfering MTRP epitopes is generally used, but a competitive binding assay may also be employed (Pound, supra).

Various methods such as Scatchard analysis in conjunction with radioimmunoassay techniques may be used to assess the affinity of antibodies for MTRP. Affinity is expressed as an  
15 association constant,  $K_a$ , which is defined as the molar concentration of MTRP-antibody complex divided by the molar concentrations of free antigen and free antibody under equilibrium conditions. The  $K_a$  determined for a preparation of polyclonal antibodies, which are heterogeneous in their affinities for multiple MTRP epitopes, represents the average affinity, or avidity, of the antibodies for MTRP. The  $K_a$  determined for a preparation of monoclonal antibodies, which are monospecific for a  
20 particular MTRP epitope, represents a true measure of affinity. High-affinity antibody preparations with  $K_a$  ranging from about  $10^9$  to  $10^{12}$  L/mole are preferred for use in immunoassays in which the MTRP-antibody complex must withstand rigorous manipulations. Low-affinity antibody preparations with  $K_a$  ranging from about  $10^6$  to  $10^7$  L/mole are preferred for use in immunopurification and similar procedures which ultimately require dissociation of MTRP, preferably in active form, from the  
25 antibody (Catty, D. (1988) Antibodies, Volume I: A Practical Approach, IRL Press, Washington, DC; Liddell, J.E. and Cryer, A. (1991) A Practical Guide to Monoclonal Antibodies, John Wiley & Sons, New York NY).

The titer and avidity of polyclonal antibody preparations may be further evaluated to determine the quality and suitability of such preparations for certain downstream applications. For  
30 example, a polyclonal antibody preparation containing at least 1-2 mg specific antibody/ml, preferably 5-10 mg specific antibody/ml, is generally employed in procedures requiring precipitation of MTRP-antibody complexes. Procedures for evaluating antibody specificity, titer, and avidity, and guidelines for antibody quality and usage in various applications, are generally available. (See, e.g., Catty, supra, and Coligan et al. supra.)

In another embodiment of the invention, the polynucleotides encoding MTRP, or any fragment or complement thereof, may be used for therapeutic purposes. In one aspect, the complement of the polynucleotide encoding MTRP may be used in situations in which it would be desirable to block the transcription of the mRNA. In particular, cells may be transformed with  
5 sequences complementary to polynucleotides encoding MTRP. Thus, complementary molecules or fragments may be used to modulate MTRP activity, or to achieve regulation of gene function. Such technology is now well known in the art, and sense or antisense oligonucleotides or larger fragments can be designed from various locations along the coding or control regions of sequences encoding MTRP.

10 Expression vectors derived from retroviruses, adenoviruses, or herpes or vaccinia viruses, or from various bacterial plasmids, may be used for delivery of nucleotide sequences to the targeted organ, tissue, or cell population. Methods which are well known to those skilled in the art can be used to construct vectors to express nucleic acid sequences complementary to the polynucleotides encoding MTRP. (See, e.g., Sambrook, supra; Ausubel, 1995, supra.)

15 Genes encoding MTRP can be turned off by transforming a cell or tissue with expression vectors which express high levels of a polynucleotide, or fragment thereof, encoding MTRP. Such constructs may be used to introduce untranslatable sense or antisense sequences into a cell. Even in the absence of integration into the DNA, such vectors may continue to transcribe RNA molecules until they are disabled by endogenous nucleases. Transient expression may last for a month or more  
20 with a non-replicating vector, and may last even longer if appropriate replication elements are part of the vector system.

As mentioned above, modifications of gene expression can be obtained by designing complementary sequences or antisense molecules (DNA, RNA, or PNA) to the control, 5', or regulatory regions of the gene encoding MTRP. Oligonucleotides derived from the transcription  
25 initiation site, e.g., between about positions -10 and +10 from the start site, may be employed. Similarly, inhibition can be achieved using triple helix base-pairing methodology. Triple helix pairing is useful because it causes inhibition of the ability of the double helix to open sufficiently for the binding of polymerases, transcription factors, or regulatory molecules. Recent therapeutic advances using triplex DNA have been described in the literature. (See, e.g., Gee, J.E. et al. (1994) in Huber,  
30 B.E. and B.I. Carr, Molecular and Immunologic Approaches, Futura Publishing, Mt. Kisco NY, pp. 163-177.) A complementary sequence or antisense molecule may also be designed to block translation of mRNA by preventing the transcript from binding to ribosomes.

Ribozymes, enzymatic RNA molecules, may also be used to catalyze the specific cleavage of RNA. The mechanism of ribozyme action involves sequence-specific hybridization of the ribozyme

molecule to complementary target RNA, followed by endonucleolytic cleavage. For example, engineered hammerhead motif ribozyme molecules may specifically and efficiently catalyze endonucleolytic cleavage of sequences encoding MTRP.

Specific ribozyme cleavage sites within any potential RNA target are initially identified by scanning the target molecule for ribozyme cleavage sites, including the following sequences: GUA, GUU, and GUC. Once identified, short RNA sequences of between 15 and 20 ribonucleotides, corresponding to the region of the target gene containing the cleavage site, may be evaluated for secondary structural features which may render the oligonucleotide inoperable. The suitability of candidate targets may also be evaluated by testing accessibility to hybridization with complementary oligonucleotides using ribonuclease protection assays.

Complementary ribonucleic acid molecules and ribozymes of the invention may be prepared by any method known in the art for the synthesis of nucleic acid molecules. These include techniques for chemically synthesizing oligonucleotides such as solid phase phosphoramidite chemical synthesis. Alternatively, RNA molecules may be generated by in vitro and in vivo transcription of DNA sequences encoding MTRP. Such DNA sequences may be incorporated into a wide variety of vectors with suitable RNA polymerase promoters such as T7 or SP6. Alternatively, these cDNA constructs that synthesize complementary RNA, constitutively or inducibly, can be introduced into cell lines, cells, or tissues.

RNA molecules may be modified to increase intracellular stability and half-life. Possible modifications include, but are not limited to, the addition of flanking sequences at the 5' and/or 3' ends of the molecule, or the use of phosphorothioate or 2' O-methyl rather than phosphodiesterase linkages within the backbone of the molecule. This concept is inherent in the production of PNAs and can be extended in all of these molecules by the inclusion of nontraditional bases such as inosine, queosine, and wybutosine, as well as acetyl-, methyl-, thio-, and similarly modified forms of adenine, cytidine, guanine, thymine, and uridine which are not as easily recognized by endogenous endonucleases.

Many methods for introducing vectors into cells or tissues are available and equally suitable for use in vivo, in vitro, and ex vivo. For ex vivo therapy, vectors may be introduced into stem cells taken from the patient and clonally propagated for autologous transplant back into that same patient. Delivery by transfection, by liposome injections, or by polycationic amino polymers may be achieved using methods which are well known in the art. (See, e.g., Goldman, C.K. et al. (1997) Nat. Biotechnol. 15:462-466.)

Any of the therapeutic methods described above may be applied to any subject in need of such therapy, including, for example, mammals such as humans, dogs, cats, cows, horses, rabbits, and monkeys.

An additional embodiment of the invention relates to the administration of a pharmaceutical or sterile composition, in conjunction with a pharmaceutically acceptable carrier, for any of the therapeutic effects discussed above. Such pharmaceutical compositions may consist of MTRP, antibodies to MTRP, and mimetics, agonists, antagonists, or inhibitors of MTRP. The compositions  
5 may be administered alone or in combination with at least one other agent, such as a stabilizing compound, which may be administered in any sterile, biocompatible pharmaceutical carrier including, but not limited to, saline, buffered saline, dextrose, and water. The compositions may be administered to a patient alone, or in combination with other agents, drugs, or hormones.

The pharmaceutical compositions utilized in this invention may be administered by any  
10 number of routes including, but not limited to, oral, intravenous, intramuscular, intra-arterial, intramedullary, intrathecal, intraventricular, transdermal, subcutaneous, intraperitoneal, intranasal, enteral, topical, sublingual, or rectal means.

In addition to the active ingredients, these pharmaceutical compositions may contain suitable pharmaceutically-acceptable carriers comprising excipients and auxiliaries which facilitate processing  
15 of the active compounds into preparations which can be used pharmaceutically. Further details on techniques for formulation and administration may be found in the latest edition of Remington's Pharmaceutical Sciences (Maack Publishing, Easton PA).

Pharmaceutical compositions for oral administration can be formulated using pharmaceutically acceptable carriers well known in the art in dosages suitable for oral administration.  
20 Such carriers enable the pharmaceutical compositions to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions, and the like, for ingestion by the patient.

Pharmaceutical preparations for oral use can be obtained through combining active compounds with solid excipient and processing the resultant mixture of granules (optionally, after grinding) to obtain tablets or dragee cores. Suitable auxiliaries can be added, if desired. Suitable  
25 excipients include carbohydrate or protein fillers, such as sugars, including lactose, sucrose, mannitol, and sorbitol; starch from corn, wheat, rice, potato, or other plants; cellulose, such as methyl cellulose, hydroxypropylmethyl-cellulose, or sodium carboxymethylcellulose; gums, including arabic and tragacanth; and proteins, such as gelatin and collagen. If desired, disintegrating or solubilizing agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, and alginic acid or a salt thereof,  
30 such as sodium alginate.

Dragee cores may be used in conjunction with suitable coatings, such as concentrated sugar solutions, which may also contain gum arabic, talc, polyvinylpyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for product identification or to



characterize the quantity of active compound, i.e., dosage.

Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a coating, such as glycerol or sorbitol. Push-fit capsules can contain active ingredients mixed with fillers or binders, such as lactose or starches, lubricants, such as talc or magnesium stearate, and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid, or liquid polyethylene glycol with or without stabilizers.

Pharmaceutical formulations suitable for parenteral administration may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hanks' solution, Ringer's solution, or physiologically buffered saline. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils, such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate, triglycerides, or liposomes. Non-lipid polycationic amino polymers may also be used for delivery. Optionally, the suspension may also contain suitable stabilizers or agents to increase the solubility of the compounds and allow for the preparation of highly concentrated solutions.

For topical or nasal administration, penetrants appropriate to the particular barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

The pharmaceutical compositions of the present invention may be manufactured in a manner that is known in the art, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping, or lyophilizing processes.

The pharmaceutical composition may be provided as a salt and can be formed with many acids, including but not limited to, hydrochloric, sulfuric, acetic, lactic, tartaric, malic, and succinic acids. Salts tend to be more soluble in aqueous or other protonic solvents than are the corresponding free base forms. In other cases, the preparation may be a lyophilized powder which may contain any or all of the following: 1 mM to 50 mM histidine, 0.1% to 2% sucrose, and 2% to 7% mannitol, at a pH range of 4.5 to 5.5, that is combined with buffer prior to use.

After pharmaceutical compositions have been prepared, they can be placed in an appropriate container and labeled for treatment of an indicated condition. For administration of MTRP, such labeling would include amount, frequency, and method of administration.

Pharmaceutical compositions suitable for use in the invention include compositions wherein the active ingredients are contained in an effective amount to achieve the intended purpose. The determination of an effective dose is well within the capability of those skilled in the art.

For any compound, the therapeutically effective dose can be estimated initially either in cell culture assays, e.g., of neoplastic cells, or in animal models such as mice, rats, rabbits, dogs, or pigs. An animal model may also be used to determine the appropriate concentration range and route of administration. Such information can then be used to determine useful doses and routes for

5 administration in humans.

A therapeutically effective dose refers to that amount of active ingredient, for example MTRP or fragments thereof, antibodies of MTRP, and agonists, antagonists or inhibitors of MTRP, which ameliorates the symptoms or condition. Therapeutic efficacy and toxicity may be determined by standard pharmaceutical procedures in cell cultures or with experimental animals, such as by  
10 calculating the  $ED_{50}$  (the dose therapeutically effective in 50% of the population) or  $LD_{50}$  (the dose lethal to 50% of the population) statistics. The dose ratio of toxic to therapeutic effects is the therapeutic index, which can be expressed as the  $LD_{50}/ED_{50}$  ratio. Pharmaceutical compositions which exhibit large therapeutic indices are preferred. The data obtained from cell culture assays and animal studies are used to formulate a range of dosage for human use. The dosage contained in such  
15 compositions is preferably within a range of circulating concentrations that includes the  $ED_{50}$  with little or no toxicity. The dosage varies within this range depending upon the dosage form employed, the sensitivity of the patient, and the route of administration.

The exact dosage will be determined by the practitioner, in light of factors related to the subject requiring treatment. Dosage and administration are adjusted to provide sufficient levels of the  
20 active moiety or to maintain the desired effect. Factors which may be taken into account include the severity of the disease state, the general health of the subject, the age, weight, and gender of the subject, time and frequency of administration, drug combination(s), reaction sensitivities, and response to therapy. Long-acting pharmaceutical compositions may be administered every 3 to 4 days, every week, or biweekly depending on the half-life and clearance rate of the particular  
25 formulation.

Normal dosage amounts may vary from about 0.1  $\mu$ g to 100,000  $\mu$ g, up to a total dose of about 1 gram, depending upon the route of administration. Guidance as to particular dosages and methods of delivery is provided in the literature and generally available to practitioners in the art. Those skilled in the art will employ different formulations for nucleotides than for proteins or their  
30 inhibitors. Similarly, delivery of polynucleotides or polypeptides will be specific to particular cells, conditions, locations, etc.

## DIAGNOSTICS

In another embodiment, antibodies which specifically bind MTRP may be used for the diagnosis of disorders characterized by expression of MTRP, or in assays to monitor patients being

treated with MTRP or agonists, antagonists, or inhibitors of MTRP. Antibodies useful for diagnostic purposes may be prepared in the same manner as described above for therapeutics. Diagnostic assays for MTRP include methods which utilize the antibody and a label to detect MTRP in human body fluids or in extracts of cells or tissues. The antibodies may be used with or without modification, and  
5 may be labeled by covalent or non-covalent attachment of a reporter molecule. A wide variety of reporter molecules, several of which are described above, are known in the art and may be used.

A variety of protocols for measuring MTRP, including ELISAs, RIAs, and FACS, are known in the art and provide a basis for diagnosing altered or abnormal levels of MTRP expression. Normal or standard values for MTRP expression are established by combining body fluids or cell extracts  
10 taken from normal mammalian subjects, for example, human subjects, with antibody to MTRP under conditions suitable for complex formation. The amount of standard complex formation may be quantitated by various methods, such as photometric means. Quantities of MTRP expressed in subject, control, and disease samples from biopsied tissues are compared with the standard values. Deviation between standard and subject values establishes the parameters for diagnosing disease.

15 In another embodiment of the invention, the polynucleotides encoding MTRP may be used for diagnostic purposes. The polynucleotides which may be used include oligonucleotide sequences, complementary RNA and DNA molecules, and PNAs. The polynucleotides may be used to detect and quantify gene expression in biopsied tissues in which expression of MTRP may be correlated with disease. The diagnostic assay may be used to determine absence, presence, and excess  
20 expression of MTRP, and to monitor regulation of MTRP levels during therapeutic intervention.

In one aspect, hybridization with PCR probes which are capable of detecting polynucleotide sequences, including genomic sequences, encoding MTRP or closely related molecules may be used to identify nucleic acid sequences which encode MTRP. The specificity of the probe, whether it is made from a highly specific region, e.g., the 5' regulatory region, or from a less specific region, e.g., a  
25 conserved motif, and the stringency of the hybridization or amplification will determine whether the probe identifies only naturally occurring sequences encoding MTRP, allelic variants, or related sequences.

Probes may also be used for the detection of related sequences, and may have at least 50% sequence identity to any of the MTRP encoding sequences. The hybridization probes of the subject  
30 invention may be DNA or RNA and may be derived from the sequence of SEQ ID NO:18-34 or from genomic sequences including promoters, enhancers, and introns of the MTRP gene.

Means for producing specific hybridization probes for DNAs encoding MTRP include the cloning of polynucleotide sequences encoding MTRP or MTRP derivatives into vectors for the production of mRNA probes. Such vectors are known in the art, are commercially available, and may

be used to synthesize RNA probes in vitro by means of the addition of the appropriate RNA polymerases and the appropriate labeled nucleotides. Hybridization probes may be labeled by a variety of reporter groups, for example, by radionuclides such as  $^{32}\text{P}$  or  $^{35}\text{S}$ , or by enzymatic labels, such as alkaline phosphatase coupled to the probe via avidin/biotin coupling systems, and the like.

- 5 Polynucleotide sequences encoding MTRP may be used for the diagnosis of disorders associated with expression of MTRP. Examples of such disorders include, but are not limited to, a membrane transport disorder such as cystinuria, dibasicaminoaciduria, hypercystinuria, lysinuria, hartnup disease, tryptophan malabsorption, methionine malabsorption, histidinuria, iminoglycinuria, dicarboxylicaminoaciduria, cystinosis, renal glycosuria, glucose-galactose malabsorption, familial
- 10 hypercholesterolemia, hypouricemia, familial hypophosphatemic rickets, congenital chloridorrhea, cystic fibrosis, familial goiter, distal renal tubular acidosis, Menkes' disease, lethal diarrhea, nephrogenic diabetes insipidus, juvenile pernicious anemia, folate malabsorption, adrenoleukodystrophy, hereditary myoglobinuria, Zellweger syndrome, hyperinsulinemic hypoglycemia, akinesia, amyotrophic lateral sclerosis, ataxia telangiectasia, cystic fibrosis, Becker's
- 15 muscular dystrophy, Bell's palsy, Charcot-Marie Tooth disease, diabetes mellitus, diabetes insipidus, diabetic neuropathy, Duchenne muscular dystrophy, hyperkalemic periodic paralysis, normokalemic periodic paralysis, Parkinson's disease, malignant hyperthermia, multidrug resistance, myasthenia gravis, myotonic dystrophy, catatonia, tardive dyskinesia, dystonias, peripheral neuropathy, cerebral neoplasms, and prostate cancer; a cardiac disorder associated with transport such as angina,
- 20 bradyarrhythmia, tachyarrhythmia, hypertension, Long QT syndrome, myocarditis, cardiomyopathy, nemaline myopathy, centronuclear myopathy, lipid myopathy, mitochondrial myopathy, thyrotoxic myopathy, ethanol myopathy, dermatomyositis, inclusion body myositis, infectious myositis, and polymyositis; a neurological disorder associated with transport such as Alzheimer's disease, amnesia, bipolar disorder, dementia, depression, epilepsy, Tourette's disorder, paranoid psychoses, and
- 25 schizophrenia; and an other disorder associated with transport such as neurofibromatosis, postherpetic neuralgia, trigeminal neuropathy, sarcoidosis, sickle cell anemia, Wilson's disease, cataracts, infertility, pulmonary artery stenosis, sensorineural autosomal deafness, hyperglycemia, hypoglycemia, Grave's disease, goiter, Cushing's disease, Addison's disease, glucose-galactose malabsorption syndrome, and hypercholesterolemia; an immune/inflammatory disorder such as
- 30 acquired immunodeficiency syndrome (AIDS), Addison's disease, adult respiratory distress syndrome, allergies, ankylosing spondylitis, amyloidosis, anemia, asthma, atherosclerosis, autoimmune hemolytic anemia, autoimmune thyroiditis, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), bronchitis, cholecystitis, contact dermatitis, Crohn's disease, atopic dermatitis, dermatomyositis, diabetes mellitus, emphysema, episodic lymphopenia

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with lymphocytotoxins, erythroblastosis fetalis, erythema nodosum, atrophic gastritis, glomerulonephritis, Goodpasture's syndrome, gout, Graves' disease, Hashimoto's thyroiditis, hypereosinophilia, irritable bowel syndrome, multiple sclerosis, myasthenia gravis, myocardial or pericardial inflammation, osteoarthritis, osteoporosis, pancreatitis, polymyositis, psoriasis, Reiter's syndrome, rheumatoid arthritis, scleroderma, Sjögren's syndrome, systemic anaphylaxis, systemic lupus erythematosus, systemic sclerosis, thrombocytopenic purpura, ulcerative colitis, uveitis, Werner syndrome, complications of cancer, hemodialysis, and extracorporeal circulation; a viral, bacterial, fungal, parasitic, protozoal, or helminthic infection; and trauma; a cell proliferative disorder such as actinic keratosis, arteriosclerosis, atherosclerosis, bursitis, cirrhosis, hepatitis, mixed connective tissue disease (MCTD), myelofibrosis, paroxysmal nocturnal hemoglobinuria, polycythemia vera, psoriasis, primary thrombocythemia; and a cancer including adenocarcinoma, leukemia, lymphoma, melanoma, myeloma, sarcoma, teratocarcinoma; and, in particular, a cancer of the adrenal gland, bladder, bone, bone marrow, brain, breast, cervix, gall bladder, ganglia, gastrointestinal tract, heart, kidney, liver, lung, muscle, ovary, pancreas, parathyroid, penis, prostate, salivary glands, skin, spleen, testis, thymus, thyroid, and uterus. The polynucleotide sequences encoding MTRP may be used in Southern or northern analysis, dot blot, or other membrane-based technologies; in PCR technologies; in dipstick, pin, and multiformat ELISA-like assays; and in microarrays utilizing fluids or tissues from patients to detect altered MTRP expression. Such qualitative or quantitative methods are well known in the art.

In a particular aspect, the nucleotide sequences encoding MTRP may be useful in assays that detect the presence of associated disorders, particularly those mentioned above. The nucleotide sequences encoding MTRP may be labeled by standard methods and added to a fluid or tissue sample from a patient under conditions suitable for the formation of hybridization complexes. After a suitable incubation period, the sample is washed and the signal is quantified and compared with a standard value. If the amount of signal in the patient sample is significantly altered in comparison to a control sample then the presence of altered levels of nucleotide sequences encoding MTRP in the sample indicates the presence of the associated disorder. Such assays may also be used to evaluate the efficacy of a particular therapeutic treatment regimen in animal studies, in clinical trials, or to monitor the treatment of an individual patient.

In order to provide a basis for the diagnosis of a disorder associated with expression of MTRP, a normal or standard profile for expression is established. This may be accomplished by combining body fluids or cell extracts taken from normal subjects, either animal or human, with a sequence, or a fragment thereof, encoding MTRP, under conditions suitable for hybridization or amplification. Standard hybridization may be quantified by comparing the values obtained from

normal subjects with values from an experiment in which a known amount of a substantially purified polynucleotide is used. Standard values obtained in this manner may be compared with values obtained from samples from patients who are symptomatic for a disorder. Deviation from standard values is used to establish the presence of a disorder.

5        Once the presence of a disorder is established and a treatment protocol is initiated, hybridization assays may be repeated on a regular basis to determine if the level of expression in the patient begins to approximate that which is observed in the normal subject. The results obtained from successive assays may be used to show the efficacy of treatment over a period ranging from several days to months.

10        With respect to cancer, the presence of an abnormal amount of transcript (either under- or overexpressed) in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development  
15        or further progression of the cancer.

Additional diagnostic uses for oligonucleotides designed from the sequences encoding MTRP may involve the use of PCR. These oligomers may be chemically synthesized, generated enzymatically, or produced in vitro. Oligomers will preferably contain a fragment of a polynucleotide encoding MTRP, or a fragment of a polynucleotide complementary to the polynucleotide encoding  
20        MTRP, and will be employed under optimized conditions for identification of a specific gene or condition. Oligomers may also be employed under less stringent conditions for detection or quantification of closely related DNA or RNA sequences.

Methods which may also be used to quantify the expression of MTRP include radiolabeling or biotinylating nucleotides, coamplification of a control nucleic acid, and interpolating results from  
25        standard curves. (See, e.g., Melby, P.C. et al. (1993) J. Immunol. Methods 159:235-244; Duplaa, C. et al. (1993) Anal. Biochem. 212:229-236.) The speed of quantitation of multiple samples may be accelerated by running the assay in a high-throughput format where the oligomer of interest is presented in various dilutions and a spectrophotometric or colorimetric response gives rapid quantitation.

30        In further embodiments, oligonucleotides or longer fragments derived from any of the polynucleotide sequences described herein may be used as targets in a microarray. The microarray can be used to monitor the expression level of large numbers of genes simultaneously and to identify genetic variants, mutations, and polymorphisms. This information may be used to determine gene function, to understand the genetic basis of a disorder, to diagnose a disorder, and to develop and

monitor the activities of therapeutic agents.

Microarrays may be prepared, used, and analyzed using methods known in the art. (See, e.g., Brennan, T.M. et al. (1995) U.S. Patent No. 5,474,796; Schena, M. et al. (1996) Proc. Natl. Acad. Sci. USA 93:10614-10619; Baldeschweiler et al. (1995) PCT application WO95/251116; Shalon, D. et al. (1995) PCT application WO95/35505; Heller, R.A. et al. (1997) Proc. Natl. Acad. Sci. USA 94:2150-2155; and Heller, M.J. et al. (1997) U.S. Patent No. 5,605,662.)

In another embodiment of the invention, nucleic acid sequences encoding MTRP may be used to generate hybridization probes useful in mapping the naturally occurring genomic sequence. The sequences may be mapped to a particular chromosome, to a specific region of a chromosome, or to artificial chromosome constructions, e.g., human artificial chromosomes (HACs), yeast artificial chromosomes (YACs), bacterial artificial chromosomes (BACs), bacterial P1 constructions, or single chromosome cDNA libraries. (See, e.g., Harrington, J.J. et al. (1997) Nat. Genet. 15:345-355; Price, C.M. (1993) Blood Rev. 7:127-134; and Trask, B.J. (1991) Trends Genet. 7:149-154.)

Fluorescent in situ hybridization (FISH) may be correlated with other physical chromosome mapping techniques and genetic map data. (See, e.g., Heinz-Ulrich, et al. (1995) in Meyers, supra, pp. 965-968.) Examples of genetic map data can be found in various scientific journals or at the Online Mendelian Inheritance in Man (OMIM) World Wide Web site. Correlation between the location of the gene encoding MTRP on a physical chromosomal map and a specific disorder, or a predisposition to a specific disorder, may help define the region of DNA associated with that disorder. The nucleotide sequences of the invention may be used to detect differences in gene sequences among normal, carrier, and affected individuals.

In situ hybridization of chromosomal preparations and physical mapping techniques, such as linkage analysis using established chromosomal markers, may be used for extending genetic maps. Often the placement of a gene on the chromosome of another mammalian species, such as mouse, may reveal associated markers even if the number or arm of a particular human chromosome is not known. New sequences can be assigned to chromosomal arms by physical mapping. This provides valuable information to investigators searching for disease genes using positional cloning or other gene discovery techniques. Once the disease or syndrome has been crudely localized by genetic linkage to a particular genomic region, e.g., ataxia-telangiectasia to 11q22-23, any sequences mapping to that area may represent associated or regulatory genes for further investigation. (See, e.g., Gatti, R.A. et al. (1988) Nature 336:577-580.) The nucleotide sequence of the subject invention may also be used to detect differences in the chromosomal location due to translocation, inversion, etc., among normal, carrier, or affected individuals.

In another embodiment of the invention, MTRP, its catalytic or immunogenic fragments, or

oligopeptides thereof can be used for screening libraries of compounds in any of a variety of drug screening techniques. The fragment employed in such screening may be free in solution, affixed to a solid support, borne on a cell surface, or located intracellularly. The formation of binding complexes between MTRP and the agent being tested may be measured.

5 Another technique for drug screening provides for high throughput screening of compounds having suitable binding affinity to the protein of interest. (See, e.g., Geysen, et al. (1984) PCT application WO84/03564.) In this method, large numbers of different small test compounds are synthesized on a solid substrate. The test compounds are reacted with MTRP, or fragments thereof, and washed. Bound MTRP is then detected by methods well known in the art. Purified MTRP can  
10 also be coated directly onto plates for use in the aforementioned drug screening techniques. Alternatively, non-neutralizing antibodies can be used to capture the peptide and immobilize it on a solid support.

In another embodiment, one may use competitive drug screening assays in which neutralizing antibodies capable of binding MTRP specifically compete with a test compound for binding MTRP.  
15 In this manner, antibodies can be used to detect the presence of any peptide which shares one or more antigenic determinants with MTRP.

In additional embodiments, the nucleotide sequences which encode MTRP may be used in any molecular biology techniques that have yet to be developed, provided the new techniques rely on properties of nucleotide sequences that are currently known, including, but not limited to, such  
20 properties as the triplet genetic code and specific base pair interactions.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific  
25 embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

The disclosures of all patents, applications, and publications mentioned above and below, in particular U.S. Ser. No. [Attorney Docket No. PF-0633 P, filed November 4, 1998], U.S. Ser. No. [Attorney Docket No. PF-0645 P, filed November 24, 1998], U.S. Ser. No. [Attorney Docket No. PF-0657 P, filed December 22, 1998], and U.S. Ser. No. 60/121,896, are hereby expressly incorporated  
30 by reference.

## EXAMPLES

### I. Construction of cDNA Libraries

RNA was purchased from Clontech or isolated from tissues described in Table 4. Some



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tissues were homogenized and lysed in guanidinium isothiocyanate, while others were homogenized and lysed in phenol or in a suitable mixture of denaturants, such as TRIZOL (Life Technologies), a monophasic solution of phenol and guanidine isothiocyanate. The resulting lysates were centrifuged over CsCl cushions or extracted with chloroform. RNA was precipitated from the lysates with either isopropanol or sodium acetate and ethanol, or by other routine methods.

Phenol extraction and precipitation of RNA were repeated as necessary to increase RNA purity. In some cases, RNA was treated with DNase. For most libraries, poly(A<sup>+</sup>) RNA was isolated using oligo d(T)-coupled paramagnetic particles (Promega), OLIGOTEX latex particles (QIAGEN, Chatsworth CA), or an OLIGOTEX mRNA purification kit (QIAGEN). Alternatively, RNA was isolated directly from tissue lysates using other RNA isolation kits, e.g., the POLY(A)PURE mRNA purification kit (Ambion, Austin TX).

In some cases, Stratagene was provided with RNA and constructed the corresponding cDNA libraries. Otherwise, cDNA was synthesized and cDNA libraries were constructed with the UNIZAP vector system (Stratagene) or SUPERScript plasmid system (Life Technologies), using the recommended procedures or similar methods known in the art. (See, e.g., Ausubel, 1997, *supra*, units 5.1-6.6.) Reverse transcription was initiated using oligo d(T) or random primers. Synthetic oligonucleotide adapters were ligated to double stranded cDNA, and the cDNA was digested with the appropriate restriction enzyme or enzymes. For most libraries, the cDNA was size-selected (300-1000 bp) using SEPHACRYL S1000, SEPHAROSE CL2B, or SEPHAROSE CL4B column chromatography (Amersham Pharmacia Biotech) or preparative agarose gel electrophoresis. cDNAs were ligated into compatible restriction enzyme sites of the polylinker of a suitable plasmid, e.g., PBLUESCRIPT plasmid (Stratagene), PSPORT1 plasmid (Life Technologies), or pINCY (Incyte Pharmaceuticals, Palo Alto CA). Recombinant plasmids were transformed into competent *E. coli* cells including XL1-Blue, XL1-BlueMRF, or SOLR from Stratagene or DH5 $\alpha$ , DH10B, or ElectroMAX DH10B from Life Technologies.

## II. Isolation of cDNA Clones

Plasmids were recovered from host cells by *in vivo* excision using the UNIZAP vector system (Stratagene) or by cell lysis. Plasmids were purified using at least one of the following: a Magic or WIZARD Minipreps DNA purification system (Promega); an AGTC Miniprep purification kit (Edge Biosystems, Gaithersburg MD); and QIAWELL 8 Plasmid, QIAWELL 8 Plus Plasmid, QIAWELL 8 Ultra Plasmid purification systems or the R.E.A.L. PREP 96 plasmid purification kit from QIAGEN. Following precipitation, plasmids were resuspended in 0.1 ml of distilled water and stored, with or without lyophilization, at 4°C.

Alternatively, plasmid DNA was amplified from host cell lysates using direct link PCR in a

high-throughput format (Rao, V.B. (1994) Anal. Biochem. 216:1-14). Host cell lysis and thermal cycling steps were carried out in a single reaction mixture. Samples were processed and stored in 384-well plates, and the concentration of amplified plasmid DNA was quantified fluorometrically using PICOGREEN dye (Molecular Probes, Eugene OR) and a FLUOROSKAN II fluorescence scanner (Labsystems Oy, Helsinki, Finland).

### III. Sequencing and Analysis

cDNA sequencing reactions were processed using standard methods or high-throughput instrumentation such as the ABI CATALYST 800 (Perkin-Elmer) thermal cycler or the PTC-200 thermal cycler (MJ Research) in conjunction with the HYDRA microdispenser (Robbins Scientific) or the MICROLAB 2200 (Hamilton) liquid transfer system. cDNA sequencing reactions were prepared using reagents provided by Amersham Pharmacia Biotech or supplied in ABI sequencing kits such as the ABI PRISM BIGDYE Terminator cycle sequencing ready reaction kit (Perkin-Elmer). Electrophoretic separation of cDNA sequencing reactions and detection of labeled polynucleotides were carried out using the MEGABACE 1000 DNA sequencing system (Molecular Dynamics); the ABI PRISM 373 or 377 sequencing system (Perkin-Elmer) in conjunction with standard ABI protocols and base calling software; or other sequence analysis systems known in the art. Reading frames within the cDNA sequences were identified using standard methods (reviewed in Ausubel, 1997, supra, unit 7.7). Some of the cDNA sequences were selected for extension using the techniques disclosed in Example V.

The polynucleotide sequences derived from cDNA sequencing were assembled and analyzed using a combination of software programs which utilize algorithms well known to those skilled in the art. Table 5 summarizes the tools, programs, and algorithms used and provides applicable descriptions, references, and threshold parameters. The first column of Table 5 shows the tools, programs, and algorithms used, the second column provides brief descriptions thereof, the third column presents appropriate references, all of which are incorporated by reference herein in their entirety, and the fourth column presents, where applicable, the scores, probability values, and other parameters used to evaluate the strength of a match between two sequences (the higher the score, the greater the homology between two sequences). Sequences were analyzed using MACDNASIS PRO software (Hitachi Software Engineering, South San Francisco CA) and LASERGENE software (DNASTAR). Polynucleotide and polypeptide sequence alignments were generated using the default parameters specified by the clustal algorithm as incorporated into the MEGALIGN multisequence alignment program (DNASTAR), which also calculates the percent identity between aligned sequences.

The polynucleotide sequences were validated by removing vector, linker, and polyA

sequences and by masking ambiguous bases, using algorithms and programs based on BLAST, dynamic programming, and dinucleotide nearest neighbor analysis. The sequences were then queried against a selection of public databases such as the GenBank primate, rodent, mammalian, vertebrate, and eukaryote databases, and BLOCKS, PRINTS, DOMO, PRODOM, and PFAM to acquire  
5 annotation using programs based on BLAST, FASTA, and BLIMPS. The sequences were assembled into full length polynucleotide sequences using programs based on Phred, Phrap, and Consed, and were screened for open reading frames using programs based on GeneMark, BLAST, and FASTA. The full length polynucleotide sequences were translated to derive the corresponding full length amino acid sequences, and these full length sequences were subsequently analyzed by querying  
10 against databases such as the GenBank databases (described above), SwissProt, BLOCKS, PRINTS, DOMO, PRODOM, Prosite, and Hidden Markov Model (HMM)-based protein family databases such as PFAM. HMM is a probabilistic approach which analyzes consensus primary structures of gene families. (See, e.g., Eddy, S.R. (1996) Curr. Opin. Struct. Biol. 6:361-365.)

The programs described above for the assembly and analysis of full length polynucleotide and  
15 amino acid sequences were also used to identify polynucleotide sequence fragments from SEQ ID NO:18-34. Fragments from about 20 to about 4000 nucleotides which are useful in hybridization and amplification technologies were described in The Invention section above.

#### IV. Northern Analysis

Northern analysis is a laboratory technique used to detect the presence of a transcript of a  
20 gene and involves the hybridization of a labeled nucleotide sequence to a membrane on which RNAs from a particular cell type or tissue have been bound. (See, e.g., Sambrook, *supra*, ch. 7; Ausubel, 1995, *supra*, ch. 4 and 16.)

Analogous computer techniques applying BLAST were used to search for identical or related molecules in nucleotide databases such as GenBank or LIFESEQ (Incyte Pharmaceuticals). This  
25 analysis is much faster than multiple membrane-based hybridizations. In addition, the sensitivity of the computer search can be modified to determine whether any particular match is categorized as exact or similar. The basis of the search is the product score, which is defined as:

$$\frac{\% \text{ sequence identity} \times \% \text{ maximum BLAST score}}{100}$$

30 The product score takes into account both the degree of similarity between two sequences and the length of the sequence match. For example, with a product score of 40, the match will be exact within a 1% to 2% error, and, with a product score of 70, the match will be exact. Similar molecules are usually identified by selecting those which show product scores between 15 and 40, although lower scores may identify related molecules.

The results of northern analyses are reported as a percentage distribution of libraries in which the transcript encoding MTRP occurred. Analysis involved the categorization of cDNA libraries by organ/tissue and disease. The organ/tissue categories included cardiovascular, dermatologic, developmental, endocrine, gastrointestinal, hematopoietic/immune, musculoskeletal, nervous, reproductive, and urologic. The disease/condition categories included cancer, inflammation, trauma, cell proliferation, neurological, and pooled. For each category, the number of libraries expressing the sequence of interest was counted and divided by the total number of libraries across all categories. Percentage values of tissue-specific and disease- or condition-specific expression are reported in Table 3.

#### 10 V. Extension of MTRP Encoding Polynucleotides

The full length nucleic acid sequences of SEQ ID NO:18-34 were produced by extension of an appropriate fragment of the full length molecule using oligonucleotide primers designed from this fragment. One primer was synthesized to initiate 5' extension of the known fragment, and the other primer, to initiate 3' extension of the known fragment. The initial primers were designed using  
15 OLIGO 4.06 software (National Biosciences), or another appropriate program, to be about 22 to 30 nucleotides in length, to have a GC content of about 50% or more, and to anneal to the target sequence at temperatures of about 68°C to about 72°C. Any stretch of nucleotides which would result in hairpin structures and primer-primer dimerizations was avoided.

Selected human cDNA libraries were used to extend the sequence. If more than one  
20 extension was necessary or desired, additional or nested sets of primers were designed.

High fidelity amplification was obtained by PCR using methods well known in the art. PCR was performed in 96-well plates using the PTC-200 thermal cycler (MJ Research, Inc.). The reaction mix contained DNA template, 200 nmol of each primer, reaction buffer containing  $Mg^{2+}$ ,  $(NH_4)_2SO_4$ , and  $\beta$ -mercaptoethanol, Taq DNA polymerase (Amersham Pharmacia Biotech), ELONGASE enzyme  
25 (Life Technologies), and Pfu DNA polymerase (Stratagene), with the following parameters for primer pair PCI A and PCI B: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 60°C, 1 min; Step 4: 68°C, 2 min; Step 5: Steps 2, 3, and 4 repeated 20 times; Step 6: 68°C, 5 min; Step 7: storage at 4°C. In the alternative, the parameters for primer pair T7 and SK+ were as follows: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 57°C, 1 min; Step 4: 68°C, 2 min; Step 5: Steps 2, 3, and 4 repeated 20 times;  
30 Step 6: 68°C, 5 min; Step 7: storage at 4°C.

The concentration of DNA in each well was determined by dispensing 100  $\mu$ l PICOGREEN quantitation reagent (0.25% (v/v) PICOGREEN; Molecular Probes, Eugene OR) dissolved in 1X TE and 0.5  $\mu$ l of undiluted PCR product into each well of an opaque fluorimeter plate (Corning Costar, Acton MA), allowing the DNA to bind to the reagent. The plate was scanned in a Fluoroskan II

(Labsystems Oy, Helsinki, Finland) to measure the fluorescence of the sample and to quantify the concentration of DNA. A 5  $\mu$ l to 10  $\mu$ l aliquot of the reaction mixture was analyzed by electrophoresis on a 1 % agarose mini-gel to determine which reactions were successful in extending the sequence.

5 The extended nucleotides were desalted and concentrated, transferred to 384-well plates, digested with CviJI cholera virus endonuclease (Molecular Biology Research, Madison WI), and sonicated or sheared prior to religation into pUC 18 vector (Amersham Pharmacia Biotech). For shotgun sequencing, the digested nucleotides were separated on low concentration (0.6 to 0.8%) agarose gels, fragments were excised, and agar digested with Agar ACE (Promega). Extended clones  
10 were religated using T4 ligase (New England Biolabs, Beverly MA) into pUC 18 vector (Amersham Pharmacia Biotech), treated with Pfu DNA polymerase (Stratagene) to fill-in restriction site overhangs, and transfected into competent *E. coli* cells. Transformed cells were selected on antibiotic-containing media, individual colonies were picked and cultured overnight at 37°C in 384-well plates in LB/2x carb liquid media.

15 The cells were lysed, and DNA was amplified by PCR using Taq DNA polymerase (Amersham Pharmacia Biotech) and Pfu DNA polymerase (Stratagene) with the following parameters: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 60°C, 1 min; Step 4: 72°C, 2 min; Step 5: steps 2, 3, and 4 repeated 29 times; Step 6: 72°C, 5 min; Step 7: storage at 4°C. DNA was quantified by PICOGREEN reagent (Molecular Probes) as described above. Samples with low DNA  
20 recoveries were reamplified using the same conditions as described above. Samples were diluted with 20% dimethylsulfoxide (1:2, v/v), and sequenced using DYENAMIC energy transfer sequencing primers and the DYENAMIC DIRECT kit (Amersham Pharmacia Biotech) or the ABI PRISM BIGDYE Terminator cycle sequencing ready reaction kit (Perkin-Elmer).

In like manner, the nucleotide sequences of SEQ ID NO:18-34 are used to obtain 5' regulatory sequences using the procedure above, oligonucleotides designed for such extension, and an appropriate genomic library.

#### VI. Labeling and Use of Individual Hybridization Probes

Hybridization probes derived from SEQ ID NO:18-34 are employed to screen cDNAs, genomic DNAs, or mRNAs. Although the labeling of oligonucleotides, consisting of about 20 base  
30 pairs, is specifically described, essentially the same procedure is used with larger nucleotide fragments. Oligonucleotides are designed using state-of-the-art software such as OLIGO 4.06 software (National Biosciences) and labeled by combining 50 pmol of each oligomer, 250  $\mu$ Ci of [ $\gamma$ -<sup>32</sup>P] adenosine triphosphate (Amersham Pharmacia Biotech), and T4 polynucleotide kinase (DuPont NEN, Boston MA). The labeled oligonucleotides are substantially purified using a

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SEPHADEX G-25 superfine size exclusion dextran bead column (Amersham Pharmacia Biotech). An aliquot containing  $10^7$  counts per minute of the labeled probe is used in a typical membrane-based hybridization analysis of human genomic DNA digested with one of the following endonucleases: Ase I, Bgl II, Eco RI, Pst I, Xba I, or Pvu II (DuPont NEN).

5           The DNA from each digest is fractionated on a 0.7% agarose gel and transferred to nylon membranes (Nytran Plus, Schleicher & Schuell, Durham NH). Hybridization is carried out for 16 hours at 40°C. To remove nonspecific signals, blots are sequentially washed at room temperature under conditions of up to, for example, 0.1 x saline sodium citrate and 0.5% sodium dodecyl sulfate. Hybridization patterns are visualized using autoradiography or an alternative imaging means and  
10 compared.

#### VII. Microarrays

A chemical coupling procedure and an ink jet device can be used to synthesize array elements on the surface of a substrate. (See, e.g., Baldeschweiler, *supra*.) An array analogous to a dot or slot blot may also be used to arrange and link elements to the surface of a substrate using thermal,  
15 UV, chemical, or mechanical bonding procedures. A typical array may be produced by hand or using available methods and machines and contain any appropriate number of elements. After hybridization, nonhybridized probes are removed and a scanner used to determine the levels and patterns of fluorescence. The degree of complementarity and the relative abundance of each probe which hybridizes to an element on the microarray may be assessed through analysis of the scanned  
20 images.

Full-length cDNAs, Expressed Sequence Tags (ESTs), or fragments thereof may comprise the elements of the microarray. Fragments suitable for hybridization can be selected using software well known in the art such as LASERGENE software (DNASTAR). Full-length cDNAs, ESTs, or fragments thereof corresponding to one of the nucleotide sequences of the present invention, or  
25 selected at random from a cDNA library relevant to the present invention, are arranged on an appropriate substrate, e.g., a glass slide. The cDNA is fixed to the slide using, e.g., UV cross-linking followed by thermal and chemical treatments and subsequent drying. (See, e.g., Schena, M. et al. (1995) Science 270:467-470; Shalon, D. et al. (1996) Genome Res. 6:639-645.) Fluorescent probes are prepared and used for hybridization to the elements on the substrate. The substrate is analyzed by  
30 procedures described above.

#### VIII. Complementary Polynucleotides

Sequences complementary to the MTRP-encoding sequences, or any parts thereof, are used to detect, decrease, or inhibit expression of naturally occurring MTRP. Although use of oligonucleotides comprising from about 15 to 30 base pairs is described, essentially the same

procedure is used with smaller or with larger sequence fragments. Appropriate oligonucleotides are designed using OLIGO 4.06 software (National Biosciences) and the coding sequence of MTRP. To inhibit transcription, a complementary oligonucleotide is designed from the most unique 5' sequence and used to prevent promoter binding to the coding sequence. To inhibit translation, a complementary oligonucleotide is designed to prevent ribosomal binding to the MTRP-encoding transcript.

## IX. Expression of MTRP

Expression and purification of MTRP is achieved using bacterial or virus-based expression systems. For expression of MTRP in bacteria, cDNA is subcloned into an appropriate vector containing an antibiotic resistance gene and an inducible promoter that directs high levels of cDNA transcription. Examples of such promoters include, but are not limited to, the *trp-lac (tac)* hybrid promoter and the T5 or T7 bacteriophage promoter in conjunction with the *lac* operator regulatory element. Recombinant vectors are transformed into suitable bacterial hosts, e.g., BL21(DE3). Antibiotic resistant bacteria express MTRP upon induction with isopropyl beta-D-thiogalactopyranoside (IPTG). Expression of MTRP in eukaryotic cells is achieved by infecting insect or mammalian cell lines with recombinant Autographica californica nuclear polyhedrosis virus (AcMNPV), commonly known as baculovirus. The nonessential polyhedrin gene of baculovirus is replaced with cDNA encoding MTRP by either homologous recombination or bacterial-mediated transposition involving transfer plasmid intermediates. Viral infectivity is maintained and the strong polyhedrin promoter drives high levels of cDNA transcription. Recombinant baculovirus is used to infect Spodoptera frugiperda (Sf9) insect cells in most cases, or human hepatocytes, in some cases. Infection of the latter requires additional genetic modifications to baculovirus. (See Engelhard, E.K. et al. (1994) Proc. Natl. Acad. Sci. USA 91:3224-3227; Sandig, V. et al. (1996) Hum. Gene Ther. 7:1937-1945.)

In most expression systems, MTRP is synthesized as a fusion protein with, e.g., glutathione S-transferase (GST) or a peptide epitope tag, such as FLAG or 6-His, permitting rapid, single-step, affinity-based purification of recombinant fusion protein from crude cell lysates. GST, a 26-kilodalton enzyme from Schistosoma japonicum, enables the purification of fusion proteins on immobilized glutathione under conditions that maintain protein activity and antigenicity (Amersham Pharmacia Biotech). Following purification, the GST moiety can be proteolytically cleaved from MTRP at specifically engineered sites. FLAG, an 8-amino acid peptide, enables immunoaffinity purification using commercially available monoclonal and polyclonal anti-FLAG antibodies (Eastman Kodak). 6-His, a stretch of six consecutive histidine residues, enables purification on metal-chelate resins (QIAGEN). Methods for protein expression and purification are discussed in Ausubel (1995, supra, ch. 10 and 16). Purified MTRP obtained by these methods can be used directly in the

following activity assay.

#### X. Demonstration of MTRP Activity

ATPase activity associated with MTRP can be measured by hydrolysis of radiolabeled ATP- $[\gamma\text{-}^{32}\text{P}]$ , separation of the hydrolysis products by chromatographic methods, and quantitation of the recovered  $^{32}\text{P}$  using a scintillation counter. The reaction mixture contains ATP- $[\gamma\text{-}^{32}\text{P}]$  and varying amounts of MTRP in a suitable buffer incubated at 37°C for a suitable period of time. The reaction is terminated by acid precipitation with trichloroacetic acid and then neutralized with base, and an aliquot of the reaction mixture is subjected to membrane or filter paper-based chromatography to separate the reaction products. The amount of  $^{32}\text{P}$  liberated is counted in a scintillation counter. The amount of radioactivity recovered is proportional to the ATPase activity of MTRP in the assay.

MTRP transport activity is assayed by measuring uptake of labeled substrates into *Xenopus laevis* oocytes. Oocytes at stages V and VI are injected with MTRP mRNA (10 ng per oocyte) and incubated for 3 days at 18°C in OR2 medium (82.5mM NaCl, 2.5 mM KCl, 1mM  $\text{CaCl}_2$ , 1mM  $\text{MgCl}_2$ , 1mM  $\text{Na}_2\text{HPO}_4$ , 5 mM Hepes, 3.8 mM NaOH, 50µg/ml gentamycin, pH 7.8) to allow expression of MTRP protein. Oocytes are then transferred to standard uptake medium (100mM NaCl, 2 mM KCl, 1mM  $\text{CaCl}_2$ , 1mM  $\text{MgCl}_2$ , 10 mM Hepes/Tris, pH 7.5). Uptake of various substrates (e.g., amino acids, sugars, drugs, and neurotransmitters) is initiated by adding a  $^3\text{H}$ -labeled substrate to the oocytes. After 30 minutes of incubation, uptake is terminated by washing the oocytes three times in  $\text{Na}^+$ -free medium. Incorporation of  $^3\text{H}$  is measured, and compared with controls. MTRP transport activity is proportional to the level of internalized  $^3\text{H}$ -labeled substrate.

#### XI. Functional Assays

MTRP function is assessed by expressing the sequences encoding MTRP at physiologically elevated levels in mammalian cell culture systems. cDNA is subcloned into a mammalian expression vector containing a strong promoter that drives high levels of cDNA expression. Vectors of choice include pCMV SPORT (Life Technologies) and pCR3.1 (Invitrogen, Carlsbad CA), both of which contain the cytomegalovirus promoter. 5-10 µg of recombinant vector are transiently transfected into a human cell line, for example, an endothelial or hematopoietic cell line, using either liposome formulations or electroporation. 1-2 µg of an additional plasmid containing sequences encoding a marker protein are co-transfected. Expression of a marker protein provides a means to distinguish transfected cells from nontransfected cells and is a reliable predictor of cDNA expression from the recombinant vector. Marker proteins of choice include, e.g., Green Fluorescent Protein (GFP; Clontech), CD64, or a CD64-GFP fusion protein. Flow cytometry (FCM), an automated, laser optics-based technique, is used to identify transfected cells expressing GFP or CD64-GFP and to evaluate the apoptotic state of the cells and other cellular properties. FCM detects and quantifies the uptake of



fluorescent molecules that diagnose events preceding or coincident with cell death. These events include changes in nuclear DNA content as measured by staining of DNA with propidium iodide; changes in cell size and granularity as measured by forward light scatter and 90 degree side light scatter; down-regulation of DNA synthesis as measured by decrease in bromodeoxyuridine uptake; alterations in expression of cell surface and intracellular proteins as measured by reactivity with specific antibodies; and alterations in plasma membrane composition as measured by the binding of fluorescein-conjugated Annexin V protein to the cell surface. Methods in flow cytometry are discussed in Ormerod, M.G. (1994) Flow Cytometry, Oxford, New York NY.

The influence of MTRP on gene expression can be assessed using highly purified populations of cells transfected with sequences encoding MTRP and either CD64 or CD64-GFP. CD64 and CD64-GFP are expressed on the surface of transfected cells and bind to conserved regions of human immunoglobulin G (IgG). Transfected cells are efficiently separated from nontransfected cells using magnetic beads coated with either human IgG or antibody against CD64 (DYNAL, Lake Success NY). mRNA can be purified from the cells using methods well known by those of skill in the art. Expression of mRNA encoding MTRP and other genes of interest can be analyzed by northern analysis or microarray techniques.

## **XII. Production of MTRP Specific Antibodies**

MTRP substantially purified using polyacrylamide gel electrophoresis (PAGE; see, e.g., Harrington, M.G. (1990) *Methods Enzymol.* 182:488-495), or other purification techniques, is used to immunize rabbits and to produce antibodies using standard protocols.

Alternatively, the MTRP amino acid sequence is analyzed using LASERGENE software (DNASTAR) to determine regions of high immunogenicity, and a corresponding oligopeptide is synthesized and used to raise antibodies by means known to those of skill in the art. Methods for selection of appropriate epitopes, such as those near the C-terminus or in hydrophilic regions are well described in the art. (See, e.g., Ausubel, 1995, *supra*, ch. 11.)

Typically, oligopeptides of about 15 residues in length are synthesized using an ABI 431A peptide synthesizer (Perkin-Elmer) using fmoc-chemistry and coupled to KLH (Sigma-Aldrich, St. Louis MO) by reaction with N-maleimidobenzoyl-N-hydroxysuccinimide ester (MBS) to increase immunogenicity. (See, e.g., Ausubel, 1995, *supra*.) Rabbits are immunized with the oligopeptide-KLH complex in complete Freund's adjuvant. Resulting antisera are tested for antipeptide and anti-MTRP activity by, for example, binding the peptide or MTRP to a substrate, blocking with 1% BSA, reacting with rabbit antisera, washing, and reacting with radio-iodinated goat anti-rabbit IgG.

## **XIII. Purification of Naturally Occurring MTRP Using Specific Antibodies**

Naturally occurring or recombinant MTRP is substantially purified by immunoaffinity

chromatography using antibodies specific for MTRP. An immunoaffinity column is constructed by covalently coupling anti-MTRP antibody to an activated chromatographic resin, such as CNBr-activated SEPHAROSE (Amersham Pharmacia Biotech). After the coupling, the resin is blocked and washed according to the manufacturer's instructions.

5 Media containing MTRP are passed over the immunoaffinity column, and the column is washed under conditions that allow the preferential absorbance of MTRP (e.g., high ionic strength buffers in the presence of detergent). The column is eluted under conditions that disrupt antibody/MTRP binding (e.g., a buffer of pH 2 to pH 3, or a high concentration of a chaotrope, such as urea or thiocyanate ion), and MTRP is collected.

#### 10 XIV. Identification of Molecules Which Interact with MTRP

MTRP, or biologically active fragments thereof, are labeled with <sup>125</sup>I Bolton-Hunter reagent. (See, e.g., Bolton A.E. and W.M. Hunter (1973) Biochem. J. 133:529-539.) Candidate molecules previously arrayed in the wells of a multi-well plate are incubated with the labeled MTRP, washed, and any wells with labeled MTRP complex are assayed. Data obtained using different concentrations  
15 of MTRP are used to calculate values for the number, affinity, and association of MTRP with the candidate molecules.

Various modifications and variations of the described methods and systems of the invention will be apparent to those skilled in the art without departing from the scope and spirit of the invention.  
20 Although the invention has been described in connection with certain embodiments, it should be understood that the invention as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the described modes for carrying out the invention which are obvious to those skilled in molecular biology or related fields are intended to be within the scope of the following claims.

Table 1

Protein SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
1	18	961344	BRSTTUT03	642329R1 (BRSTNOT03), 961344H1 (BRSTTUT03), 3149970H1 (ADRENON04), 3255621H1 (OVRTUN01), 4265773H1 (KIDNNOT32), 4641320H1 (PROSTMOT03), 4875558H1 (COLDNOT01)
2	19	3128782	LUNGTUT12	148511X20R1 (FIBRNGT01), 580891H1 (BRAVXT05), 1304328F1 (PLACNOT02), 1469890T6 (PANCUTUT02), 1799816T6 (COLNNOT27), 1985910R6 (LUNGAST01), 2722244F6 (LUNGTUT10), 3128782F6 (LUNGTUT12), 3128782H1 (LUNGTUT12), 3276993F6 (PROSBPT06), SBMA03256F1
3	20	1720440	BLADNOT06	744485R1 (BRAITUT01), 859118R1 (BRAITUT03), 94049T1 (ADRENOT03), 1432755R1 (BEPINON01), 1720440H1 (BLADNOT06), 1808737X11C1 (PROSTUT12), 1812106F6 (PROSTUT12), 2192988F6 (THYRTUT03), 2192988X13F1 (THYRTUT03), 2192988X14F1 (THYRTUT03), 3384757H1 (ESOGNOT04)
4	21	2274290	PROSNON01	1732422F6 (BRSTTUT08), 2098563H1 (BRAITUT02), 2274290H1 (PROSNON01), 2274290X326D2 (PROSNON01), 2598580F6 (UTFSNOT10), 2779864F6 (OVRTUT03), 2864759F6 (KIDNNOT20), 2864759T6 (KIDNNOT20), 3221871H1 (COLNNON03)
5	22	2740029	BRSTTUT14	966363H1 (BRSTNOT05), 1000112R1 (BRSTNOT03), 1647057F6 (PROSTUT09), 2740029H1 (BRSTTUT14), 2740029X309F1 (BRSTTUT14), 2740029X321F1 (BRSTTUT14), 5068692H1 (PANCNOT23), 5193978H1 (LUNLTUT04), SBOA03895D1
6	23	2414415	HNT3AZT01	1508631H1 (LUNGNOT14), 1596418F1 (BRAINOT14), 2414415F6 (HNT3AZT01), 2414415H1 (HNT3AZT01), 2414415X300D1 (HNT3AZT01), 2902794H1 (DRGCNOT01), 3080373H1 (BRAIUNT01), 3554689H1 (SYNONOT01), 3881949F6 (SPLNNOT11), 4996983H1 (MYEPTXT02)
7	24	2466714	THYRNOT08	627910R6 (KIDNNOT05), 2358261R6 (LUNGFET05), 2358464F6 (LUNGFET05), 2466714H1 (THYRNOT08), 2726053F6 (OVRTUT05), 3845383H1 (DENDNOT01), 4228854H1 (BRAMDIT01)

Table 1 (cont.)

Protein SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
8	25	2617942	GBLANOT01	1311045F6 (COLNFET02), 1375061F6 (LUNGN0T10), 1580318F6 (DUODNOT01), 2016443F6 (ENDCNOT03), 2617942F6 (GBLANOT01), 2617942H1 (GBLANOT01), 2703625H1 (OVRTUT10)
9	26	2945431	BRAITUT23	782666T6 (MYOMNOT01), 2715384T6 (THYRN0T09), 2945431F6 (BRAITUT23), 2945431H1 (BRAITUT23), 4114919F6 (UTRSTUT07)
10	27	4074113	KIDNNOT26	1754278T6 (LIVRTUT01), 1830341T6 (THP1AZT01), 2122328T6 (BRSTNOT07), 4074113F6 (KIDNNOT26), 4074113H1 (KIDNNOT26)
11	28	1413743	BRAINOT12	1413743H1 (BRAINOT12), 2643096F6 (LUNGTUT08), SBWA04580V1, SBWA04306V1, SBWA00027V1, SBWA00447V1, SBWA00075V1, SBWA03280V1, SBWA00778V1
12	29	1733477	BRSTTUT08	1733477H1 (BRSTTUT08), 1733477F6 (BRSTTUT08), 3346594F6 (BRAITUT24), 1696051F6 (COLNNOT23), SAFC01922F1, 3234341F6 (COLNUCT03), 2634476T6 (COLNTUT15), SBWA03249F1
13	30	2641908	LUNGTUT08	2641908H1 (LUNGTUT08), SASA01215F1, SASB01010F1, SASB01616F1, SASA03523F1
14	31	2656554	LUNGTUT09	2656554H1 (LUNGTUT09), 2656554F6 (LUNGTUT09), 2656554T6 (LUNGTUT09)
15	32	2719228	THYRN0T09	2719228H1 (THYRN0T09), 2719228F6 (THYRN0T09), 532553H1 (BRAINOT03), 1626110F6 (COLNPOT01), 1626488F6 (COLNPOT01), 2100947R6 (BRAITUT02), SBGA05174F1
16	33	3657824	ENDPNOT02	3657824H1 (ENDPNOT02), 2450345F6 (ENDANOT01), 2756551H1 (THP1AZS08), SCBA01425V1, 2394519T6 (THP1AZT01)
17	34	5378485	BRAXNOT01	5378485H1 (BRAXNOT01), SCAA06347V1, 1570276F1 (UTRSNOT05)

Table 2

SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences	Identification/ Homologies	Analytical Methods
1	384	S375 S34 T33 T89 T102 S161 S246 T298		E1-E2 ATPase signatures: R85-D115, T106-I128 P-type cation transporter signature: I109-I128 Transmembrane domains: I330-W351, L271-I288	E1-E2 ATPase [Mus musculus] (GI 2944187)	BLAST BLOCKS MOTIFS PFAM PRINTS
2	846	T80 S106 S22 T40 T109 S110 S141 S229 S245 S255 S288 T408 T614 T679 T707 S819 S24 S274 S293 T386 T450 T536 S568 T581 T610 T673	N301	ABC transporter signatures: F453-L467, G330-Q525, D652-Q816, L744-A758 ATP-binding (P-loop) domains: G337-T344, G659-S666	ABC transporter protein isoform [Homo sapiens] (GI 2522534)	BLAST BLOCKS MOTIFS PFAM PRINTS ProfileScan SPScan
3	511	S183 S99 S385 T387 T39 T106 S240 T376 T461 Y111 Y151 Y194 Y353	N195 N238 N258 N383	AMP-binding enzyme motif: R4-V404 AMP-binding domain signature: K91-M144 Lipocalin signature: E2-M14	Fatty acid transport protein [Homo sapiens] (GI 4206376)  Fatty acid transport protein [Mus musculus] (GI 2612939)	BLAST MOTIFS PFAM PRINTS ProfileScan

Table 2 (cont.)

SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences	Identification/ Homologies	Analytical Methods
4	718	S303 T224 T390 S501 T547 S560 S579 S623 T675 S248 S274 T326 S629 T655	N176 N229 N410	ABC transporter domain: L595-L609 ABC transporter family signatures: G483-V499, L595-D626 ABC transporter transmembrane domain: L128-M408 ABC transporter nucleotide binding domain: G483-G668 ATP/GTP-binding site motif A: G490-T497 Transmembrane domain: F123-V144	ABC transporter protein [Homo sapiens] (GI 4321407)  SMDR1 [Schistosoma mansoni] (GI 425474)	BLAST BLOCKS MOTIFS PFAM HMM
5	635	S25 T55 S128 T172 S242 S284 T378 T140 S222 S283 T286 T549	N138 N489 N498 N534	Sodium:solute symporter family signature: M61-A467, N169-A216, T172-V217, G353-I383, I430-A467 Transmembrane domains: M27-Y45, F256-A276, I430-F448, V458-G480	Sodium:solute symporter [Homo sapiens] (GI 4884550)	BLAST BLOCKS PFAM ProfileScan HMM

Table 2 (cont.)

SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences	Identification/ Homologies	Analytical Methods
6	535	T11 S61 S103 S179 S292 T305 S337 T363 S487 S502 Y109		Amino acid permeases signature: L36-K474 (from PFAM) Transmembrane domains: L76-L96, K111-Y131, S159-N176, I189-V207, N264-Y287, I422-F449, I451-W469	SLC7A8 [Homo sapiens] (GI 4581470)  Amino acid transporter (GI 3639058, SEQ ID NO:38)	BLAST BLOCKS MOTIFS PFAM
7	456	T106 S107 S215 S277 T306 T331 S419 S425		Aromatic amino acid permease signature: N53-S98 (from BLOCKS) Transmembrane domains: F47-V69, Y68-L88, T169-L191, L197-I216, S366-Y387, M330-I347, F432-I454	Aromatic amino acid transporter (GI 1840045, SEQ ID NO:39)	BLAST BLOCKS MOTIFS
8	325	T23 T29 S65 T84 S106 S133 S160		Transmembrane domains: I209-D227, I284-T307	UDP-N-acetylglucosamine transporter [Canis familiaris] (GI 3298605)	BLAST MOTIFS
9	178	S4 T22 S132 T151		ABC transporters signature: S2-G141 (from PFAM)	ABC transporter (GI 3335175, SEQ ID NO:41)	BLAST BLOCKS MOTIFS PFAM Profilescan

Table 2 (cont.)

SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences	Identification/ Homologies	Analytical Methods
10	255	T89 S107 S214		ABC transporters signature: Q45-G227 (from PFAM)	Anthracycline resistance-associated protein (ABC transporter; GI 1279457, SEQ ID NO:42)	BLAST BLOCKS MOTIFS PFAM Profilescan
11	462	T179 S11 S37 T114 S420 T174		Aromatic amino acid permease signatures: F58-A104, A243-F265, L375-K394	Transmembrane transporter [Schizosaccharomyces pombe] (GI 3367790)	BLAST MOTIFS PRINTS
12	758	T174 T251 S376 T615 S616 S633 S678 S713 S733 T138 S574 S603 T656 S687 T726 Y703	N167 N172 N614	Sulfate transporter signature: L198-T508	Transporter [Mus musculus] (GI 5359730)  Transporter [Homo sapiens] (GI 291964)	BLAST MOTIFS PFAM
13	336	T32 S99 S254 T274 S103 T104 T133 S273	N116	Transmembrane domains: L211-G230, A175-L196, W42-F61, F139-F159	Organic anion transporter OATP-B [Homo sapiens] (GI 5006263)	BLAST HMM MOTIFS
14	103	S9 S92 Y14	N81	Transmembrane domain: V22-F41	Similar to Human Na <sup>+</sup> /H <sup>+</sup> exchanger 2 (A57644) [Homo sapiens] (GI 1665827)	BLAST HMM MOTIFS



Table 2 (cont.)

SEQ ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequences	Identification/ Homologies	Analytical Methods
15	123	S21 S118 T119	N39	Signal peptide: M1-S21	Similar to Sugar transporter [Caenorhabditis elegans] (GI 3878537)	BLAST HMM MOTIFS
16	222	T83 S61 S74			<i>E. coli</i> cation transport protein (GI495778)	BLAST MOTIFS
17	111		N100		Vacuolar proton-ATPase subunit M9.2 [Homo sapiens] (GI 2584789)	BLAST MOTIFS

Table 3

Nucleotide SEQ ID NO:	Tissue Expression (Fraction of Total)	Disease or Condition (Fraction of Total)	Vector
18	Reproductive (0.292) Nervous (0.167) Hematopoietic/Immune (0.125)	Cell proliferative (0.750) Inflammation (0.208)	PSPORT1
19	Reproductive (0.264) Nervous (0.155) Hematopoietic/Immune (0.145)	Cell proliferative (0.691) Inflammation (0.236)	pINCY
20	Reproductive Nervous Gastrointestinal	Cell proliferation (0.66) Inflammation and immune response (0.24)	pINCY
21	Reproductive Nervous Gastrointestinal Hematopoietic/Immune	Cell proliferation (0.73) Inflammation and immune response (0.21)	PSPORT1
22	Nervous Reproductive	Cell proliferation (0.76) Inflammation and immune response (0.33)	pINCY
23	Reproductive (0.333) Nervous (0.296)	Cancer (0.519) Inflammation (0.185)	
24	Reproductive (0.250) Musculoskeletal (0.179) Hematopoietic/Immune (0.143)	Cancer (0.429) Inflammation (0.286)	
25	Reproductive (0.360) Gastrointestinal (0.200) Cardiovascular (0.120)	Cancer (0.520) Inflammation (0.160)	
26	Nervous (0.267) Endocrine (0.133)	Cancer (0.533) Inflammation (0.333)	

Table 3 (cont.)

Nucleotide SEQ ID NO:	Tissue Expression (Fraction of Total)	Disease or Condition (Fraction of Total)	Vector
27	Urologic (0.333) Cardiovascular (0.167) Developmental (0.167)	Cancer (0.667) Inflammation (0.167)	
28	Nervous (0.222) Hematopoietic/Immune (0.185) Reproductive (0.185)	Cell Proliferation (0.481) Inflammation (0.407)	pINCY
29	Gastrointestinal (0.286) Reproductive (0.257) Nervous (0.200)	Cell Proliferation (0.743) Inflammation (0.286)	pINCY
30	Cardiovascular (0.400) Nervous (0.200) Reproductive (0.200) Gastrointestinal (0.200)	Cell Proliferation (0.800) Inflammation (0.200)	pINCY
31	Hematopoietic/Immune (0.500) Reproductive (0.250) Cardiovascular (0.250)	Cell Proliferation (0.750) Inflammation (0.500)	pINCY
32	Gastrointestinal (0.304) Hematopoietic/Immune (0.174) Nervous (0.174)	Cell Proliferation (0.826) Inflammation (0.347)	pINCY
33	Cardiovascular (0.238) Nervous (0.190) Hematopoietic/Immune (0.143)	Cell Proliferation (0.571) Inflammation (0.473)	pINCY
34	Nervous (0.510) Cardiovascular (0.102)	Cell Proliferation (0.612) Inflammation (0.266)	pINCY

Table 4

Nucleotide SEQ ID NO:	Library	Library Comment
18	BRSTTUT03	Library was constructed using RNA isolated from breast tumor tissue removed from a 58-year-old Caucasian female during a unilateral extended simple mastectomy. Pathology indicated multicentric invasive grade 4 lobular carcinoma. The mass was identified in the upper outer quadrant, and three separate nodules were found in the lower outer quadrant of the left breast. Patient history included skin cancer, rheumatic heart disease, osteoarthritis, and tuberculosis. Family history included cerebrovascular disease, coronary artery aneurysm, breast cancer, prostate cancer, atherosclerotic coronary artery disease, and type I diabetes.
19	LUNGTUT12	Library was constructed using RNA isolated from tumorous lung tissue removed from a 70-year-old Caucasian female during a lung lobectomy of the left upper lobe. Pathology indicated grade 3 (of 4) adenocarcinoma and vascular invasion. Patient history included tobacco abuse, depressive disorder, anxiety state, and skin cancer. Family history included cerebrovascular disease, congestive heart failure, colon cancer, depressive disorder, and primary liver cancer.
20	BLADNOT06	Library was constructed using RNA isolated from posterior wall bladder tissue removed from a 66-year-old Caucasian male during a radical prostatectomy, radical cystectomy, and urinary diversion. Pathology for the associated tumor tissue indicated grade 3 transitional cell carcinoma on the anterior wall of the bladder and urothelium. Patient history included lung neoplasm. Family history included a malignant breast neoplasm, tuberculosis, cerebrovascular disease, atherosclerotic coronary artery disease, and lung cancer.
21	PROSNON01	Normalized prostate library was constructed from 4.4 million independent clones from a prostate library. Starting RNA was made from prostate tissue removed from a 28-year-old Caucasian male. The normalization and hybridization conditions were adapted from Soares, M.B. et al. (1994) Proc. Natl. Acad. Sci. USA 91:9228-9232, using a longer (19 hour) reannealing hybridization period.

Table 4 (cont.)

Nucleotide SEQ ID NO:	Library	Library Comment
22	BRSTTUT14	Library was constructed using RNA isolated from breast tumor tissue removed from a 62-year-old Caucasian female during a unilateral extended simple mastectomy. Pathology indicated an invasive grade 3 (of 4), nuclear grade 3 (of 3) adenocarcinoma, ductal type. Ductal carcinoma in situ, comedo type, comprised 60% of the tumor mass. Metastatic adenocarcinoma was identified in one (of 14) axillary lymph nodes with no perinodal extension. Tumor cells were strongly positive for estrogen receptors and weakly positive for progesterone receptors. Patient history included benign colon neoplasm, hyperlipidemia, cardiac dysrhythmia, and obesity. Family history included atherosclerotic coronary artery disease, myocardial infarction, colon cancer, ovarian cancer, lung cancer, and cerebrovascular disease.
23	HNT3AZT01	Library was constructed using RNA isolated from the hNT2 cell line (derived from a human teratocarcinoma that exhibited properties characteristic of a committed neuronal precursor). Cells were treated for three days with 0.35 micromolar 5-aza-2'-deoxycytidine (AZ).
24	THYRN0T08	Library was constructed using RNA isolated from the diseased left thyroid tissue removed from a 13-year-old Caucasian female during a complete thyroidectomy. Pathology indicated lymphocytic thyroiditis.
25	GBLANOT01	Library was constructed using RNA isolated from diseased gallbladder tissue removed from a 53-year-old Caucasian female during a cholecystectomy. Pathology indicated mild chronic cholecystitis and cholelithiasis with approximately 150 mixed gallstones. Family history included benign hypertension.
26	BRAITUT23	Library was constructed using RNA isolated from left posterior brain tumor tissue removed from a 36-year-old male during a cerebral meninges lesion excision. Pathology indicated meningioma. Family history included malignant skin melanoma, atherosclerotic coronary artery disease, hyperlipidemia, Huntington's chorea, and rheumatoid arthritis.

Table 4 (cont.)

Nucleotide SEQ ID NO:	Library	Library Comment
27	KIDNNOT26	Library was constructed using RNA isolated from left kidney medulla and cortex tissue removed from a 53-year-old Caucasian female during a nephroureterectomy. Patient history included hyperlipidemia, cardiac dysrhythmia, metrorrhagia, cerebrovascular disease, and atherosclerotic coronary artery disease.
28	BRAINOT12	Library was constructed using RNA isolated from brain tissue removed from the right frontal lobe of a 5-year-old Caucasian male during a hemispherectomy. Pathology indicated extensive polymicrogyria and mild to moderate gliosis (predominantly subpial and subcortical), which are consistent with chronic seizure disorder. The patient presented with intractable convulsive epilepsy. Family history included a cervical neoplasm.
29	BRSTTUT08	Library was constructed using RNA isolated from breast tumor tissue removed from a 45-year-old Caucasian female during unilateral extended simple mastectomy. Pathology indicated invasive nuclear grade 2-3 adenocarcinoma (ductal type), with 3 of 23 lymph nodes positive for metastatic disease. Greater than 50% of the tumor volume was in-situ, both comedo and non-comedo types. There were also positive estrogen/progesterone receptors and uninvolved tissue showing proliferative changes. Patient history included valvuloplasty of mitral valve without replacement, rheumatic mitral insufficiency, and rheumatic heart disease. Family history included acute myocardial infarction and atherosclerotic coronary artery disease and type II diabetes.

Table 4 (cont.)

Nucleotide SEQ ID NO:	Library	Library Comment
30	LUNGTUT08	<p>Library was constructed using RNA isolated from lung tumor tissue removed from a 63-year-old Caucasian male during a right upper lobectomy with fiberoptic bronchoscopy. Pathology indicated a grade 3 adenocarcinoma, forming a mass penetrating the pleura of the right upper lung lobe. The bronchial margin of the resection was free of tumor. The tissue from the superior segment of the right lower lobe lung showed multiple (2) calcified granulomas. Multiple lymph nodes were negative for tumor. In addition, budding yeast forms resembling histoplasma identified in two lymph nodes stained with GMS (silver). Patient history included atherosclerotic coronary artery disease, an acute myocardial infarction, rectal cancer, an asymptomatic abdominal aortic aneurysm, tobacco abuse, and cardiac dysrhythmia. Family history included congestive heart failure, stomach cancer, lung cancer, type II diabetes, atherosclerotic coronary artery disease, and acute myocardial infarction.</p>
31	LUNGTUT09	<p>Library was constructed RNA isolated from lung tumor tissue removed from a 68-year-old Caucasian male during segmental lung resection. Pathology indicated invasive grade 3 squamous cell carcinoma in the right upper lobe, forming an infiltrating mass involving the bronchus and the surrounding parenchyma. One (of 4) intrapulmonary peribronchial lymph nodes contained a metastatic tumor. An apical cap was identified. One (of 15) right paratracheal lower lymph nodes contained a metastatic tumor. Permanent superior mediastinal sections revealed metastatic squamous cell carcinoma in the lymph nodes. Patient history included of type II diabetes, thyroid disorder, depressive disorder, hyperlipidemia, esophageal ulcer, and tobacco use. Family history included brain cancer and atherosclerotic coronary artery disease.</p>

Table 4 (cont.)

Nucleotide SEQ ID NO:	Library	Library Comment
32	THYRNOT09	Library was constructed using RNA isolated from diseased thyroid tissue removed from an 18-year-old Caucasian female during an unilateral thyroid lobectomy and regional lymph node excision. Pathology indicated adenomatous goiter. This was associated with a follicular adenoma of the thyroid. The right neck lymph nodes displayed reactive follicular hyperplasia. The patient presented with hypophosphatemia. Patient history included compression of the brain, headache, iron deficiency anemia, active rickets, epidermal nevus syndrome (treated with lasers), and osteitis deformans. Family history included thyroid cancer, type II diabetes, benign hypertension, and nodular lymphoma.
33	ENDENOT02	Library was constructed using RNA isolated from pulmonary artery endothelial cells removed from a 10-year-old Caucasian male. The cells were treated with TNF alpha and IL-1 beta 10ng/ml each for 20 hours.
34	BRAXNOT01	Library was constructed using RNA isolated from cerebellar tissue removed from a 70-year-old male. Patient history included chronic obstructive airways disease and left ventricular failure.



Table 5

Program	Description	Reference	Parameter Threshold
ABI FACTURA	A program that removes vector sequences and masks ambiguous bases in nucleic acid sequences.	Perkin-Elmer Applied Biosystems, Foster City, CA.	
ABI/PARACEL FDF	A Fast Data Finder useful in comparing and annotating amino acid or nucleic acid sequences.	Perkin-Elmer Applied Biosystems, Foster City, CA; Paracel Inc., Pasadena, CA.	Mismatch <50%
ABI AutoAssembler	A program that assembles nucleic acid sequences.	Perkin-Elmer Applied Biosystems, Foster City, CA.	
BLAST	A Basic Local Alignment Search Tool useful in sequence similarity search for amino acid and nucleic acid sequences. BLAST includes five functions: blastp, blastn, blastx, tblastn, and tblastx.	Altschul, S.F. et al. (1990) J. Mol. Biol. 215:403-410; Altschul, S.F. et al. (1997) Nucleic Acids Res. 25: 3389-3402.	ESTs: Probability value= 1.0E-8 or less Full Length sequences: Probability value= 1.0E-10 or less
FASTA	A Pearson and Lipman algorithm that searches for similarity between a query sequence and a group of sequences of the same type. FASTA comprises at least five functions: fasta, tfasta, fastx, tfastx, and ssearch.	Pearson, W.R. and D.J. Lipman (1988) Proc. Natl. Acad. Sci. 85:2444-2448; Pearson, W.R. (1990) Methods Enzymol. 183: 63-98; and Smith, T.F. and M. S. Waterman (1981) Adv. Appl. Math. 2:482-489.	ESTs: fasta E value=1.06E-6 Assembled ESTs: fasta Identity= 95% or greater and Match length=200 bases or greater, fastx E value=1.0E-8 or less Full Length sequences: fastx score=100 or greater
BLIMPS	A BLocks IMProved Searcher that matches a sequence against those in BLOCKS, PRINTS, DOMO, PRODOM, and PFAM databases to search for gene families, sequence homology, and structural fingerprint regions.	Henikoff, S. and J.G. Henikoff, Nucl. Acid Res., 19:6565-72, 1991. J.G. Henikoff and S. Henikoff (1996) Methods Enzymol. 266:38-105; and Attwood, T.K. et al. (1997) J. Chem. Inf. Comput. Sci. 37: 417-424.	Score=1000 or greater, Ratio of Score/Strength = 0.75 or larger, and, if applicable, Probability value= 1.0E-3 or less
HMMER	An algorithm for searching a query sequence against hidden Markov model (HMM)-based databases of protein family consensus sequences, such as PFAM.	Krogh, A. et al. (1994) J. Mol. Biol., 235:1501-1531; Sonnhammer, E.L.L. et al. (1988) Nucleic Acids Res. 26:320-322.	Score=10-50 bits for PFAM hits, depending on individual protein families

Table 5 (cont.)

Program	Description	Reference	Parameter Threshold
ProfileScan	An algorithm that searches for structural and sequence motifs in protein sequences that match sequence patterns defined in Prosite.	Gribkov, M. et al. (1988) CABIOS 4:61-66; Gribkov, et al. (1989) Methods Enzymol. 183:146-159; Bairoch, A. et al. (1997) Nucleic Acids Res. 25: 217-221.	Normalized quality score > GCG-specified "HIGH" value for that particular Prosite motif. Generally, score=1.4-2.1.
Phred	A base-calling algorithm that examines automated sequencer traces with high sensitivity and probability.	Ewing, B. et al. (1998) Genome Res. 8:175-185; Ewing, B. and P. Green (1998) Genome Res. 8:186-194.	
Phrap	A Phils Revised Assembly Program including SWAT and CrossMatch, programs based on efficient implementation of the Smith-Waterman algorithm, useful in searching sequence homology and assembling DNA sequences.	Smith, T.F. and M. S. Waterman (1981) Adv. Appl. Math. 2:482-489; Smith, T.F. and M. S. Waterman (1981) J. Mol. Biol. 147:195-197; and Green, P.; University of Washington, Seattle, WA.	Score= 120 or greater, Match length= 56 or greater
Consed	A graphical tool for viewing and editing Phrap assemblies	Gordon, D. et al. (1998) Genome Res. 8:195-202.	
SPScan	A weight matrix analysis program that scans protein sequences for the presence of secretory signal peptides.	Nielson, H. et al. (1997) Protein Engineering 10:1-6; Claverie, J.M. and S. Audic (1997) CABIOS 12: 431-439.	Score=3.5 or greater
Motifs	A program that searches amino acid sequences for patterns that matched those defined in Prosite.	Bairoch et al. <u>supra</u> ; Wisconsin Package Program Manual, version 9, page M51-59, Genetics Computer Group, Madison, WI.	

What is claimed is:

1. A substantially purified polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-17 and fragments thereof.
- 5 2. A substantially purified variant having at least 90% amino acid sequence identity to the amino acid sequence of claim 1.
3. An isolated and purified polynucleotide encoding the polypeptide of claim 1.
- 10 4. An isolated and purified polynucleotide variant having at least 90% polynucleotide sequence identity to the polynucleotide of claim 3.
5. An isolated and purified polynucleotide which hybridizes under stringent conditions  
15 to the polynucleotide of claim 3.
6. An isolated and purified polynucleotide having a sequence which is complementary to the polynucleotide of claim 3.
- 20 7. A method for detecting a polynucleotide, the method comprising the steps of:
  - (a) hybridizing the polynucleotide of claim 6 to at least one nucleic acid in a sample, thereby forming a hybridization complex; and
  - (b) detecting the hybridization complex, wherein the presence of the hybridization complex correlates with the presence of the polynucleotide in the sample.
- 25 8. The method of claim 7 further comprising amplifying the polynucleotide prior to hybridization.
9. An isolated and purified polynucleotide comprising a polynucleotide sequence  
30 selected from the group consisting of SEQ ID NO:18-34 and fragments thereof.
10. An isolated and purified polynucleotide variant having at least 90% polynucleotide sequence identity to the polynucleotide of claim 9.

11. An isolated and purified polynucleotide having a sequence which is complementary to the polynucleotide of claim 9.

12. An expression vector comprising at least a fragment of the polynucleotide of claim 3.

5

13. A host cell comprising the expression vector of claim 12.

14. A method for producing a polypeptide, the method comprising the steps of:

- 10 a) culturing the host cell of claim 13 under conditions suitable for the expression of the polypeptide; and  
b) recovering the polypeptide from the host cell culture.

15. A pharmaceutical composition comprising the polypeptide of claim 1 in conjunction with a suitable pharmaceutical carrier.

15

16. A purified antibody which specifically binds to the polypeptide of claim 1.

17. A purified agonist of the polypeptide of claim 1.

20

18. A purified antagonist of the polypeptide of claim 1.

19. A method for treating or preventing a disorder associated with decreased expression or activity of MTRP, the method comprising administering to a subject in need of such treatment an effective amount of the pharmaceutical composition of claim 15.

25

20. A method for treating or preventing a disorder associated with increased expression or activity of MTRP, the method comprising administering to a subject in need of such treatment an effective amount of the antagonist of claim 18.

**1/12**

[illegible]

**FIGURE 1A**

2/12

47	F	G	S	E	M	A	S	A	I	C	E	V	H	A	S	L	D	P	S	L	S	L	F	C	S	G	S	W	E	P	1720440
181	Y	G	G	E	M	A	A	V	A	E	V	S	E	Q	L	G	K	S	L	L	K	F	C	S	G	D	L	G	P	GI 2612939	
77	G	A	V	P	P	S	T	E	H	L	D	P	L	L	K	D	A	P	K	-	H	L	P	S	C	P	D	K	G	F	1720440
211	E	S	I	L	P	D	T	Q	L	L	D	P	M	L	A	E	A	P	T	T	P	L	A	Q	A	P	G	K	G	M	GI 2612939
106	T	D	K	L	F	Y	I	Y	T	S	G	T	T	G	L	P	K	A	A	I	V	V	H	S	R	Y	Y	R	M	A	1720440
241	D	D	R	L	F	Y	I	Y	T	S	G	T	T	G	L	P	K	A	A	I	V	V	H	S	R	Y	Y	R	I	A	GI 2612939
136	A	L	V	Y	Y	G	F	R	M	R	P	N	D	I	V	Y	D	C	L	P	L	Y	H	S	A	G	N	I	V	G	1720440
271	A	F	G	H	S	Y	S	M	R	A	A	D	V	L	Y	D	C	L	P	L	Y	H	S	A	G	N	I	M	G	GI 2612939	
166	I	G	Q	C	L	L	H	G	M	T	V	V	I	R	K	K	F	S	A	S	R	F	W	D	D	C	I	K	Y	N	1720440
301	V	G	Q	C	V	I	Y	G	L	T	V	V	L	R	K	K	F	S	A	S	R	F	W	D	D	C	V	K	Y	N	GI 2612939
196	C	T	I	V	Q	Y	I	G	E	L	C	R	Y	L	L	N	Q	P	P	R	E	A	E	N	Q	H	Q	V	R	M	1720440
331	C	T	V	V	Q	Y	I	G	E	I	C	R	Y	L	L	R	Q	P	V	R	D	V	E	Q	R	H	R	V	R	L	GI 2612939

FIGURE 1B

3/12

226	A	L	G	N	G	L	R	Q	S	I	W	T	N	F	S	S	R	F	H	I	P	Q	V	A	E	F	Y	G	A	T	1720440
361	A	V	G	N	G	L	R	P	A	I	W	E	E	F	T	Q	R	F	G	V	P	Q	I	G	E	F	Y	G	A	T	GI 2612939
256	E	C	N	C	S	L	G	N	F	D	S	Q	V	G	A	C	G	F	N	S	R	I	L	S	S	V	Y	P	I	R	1720440
391	E	C	N	C	S	I	A	N	M	D	G	K	V	G	S	C	G	F	N	S	R	I	L	T	H	V	Y	P	I	R	GI 2612939
286	L	V	R	V	N	E	D	T	M	E	L	I	R	G	P	D	G	V	C	I	P	C	Q	P	G	E	P	G	Q	L	1720440
421	L	V	K	V	N	E	D	T	M	E	P	L	R	D	S	E	G	L	C	I	P	C	Q	P	G	E	P	G	L	L	GI 2612939
316	V	G	R	I	I	Q	K	D	P	L	R	R	F	D	G	Y	L	N	Q	G	A	N	N	K	K	I	A	K	D	V	1720440
451	V	G	Q	I	N	Q	Q	D	P	L	R	R	F	D	G	Y	V	S	D	S	A	T	N	K	K	I	A	H	S	V	GI 2612939
346	F	K	K	G	D	Q	A	Y	L	T	G	D	V	L	V	M	D	E	L	G	Y	L	Y	F	R	D	R	T	G	D	1720440
481	F	R	K	G	D	S	A	Y	L	S	G	D	V	L	V	M	D	E	L	G	Y	M	Y	F	R	D	R	S	G	D	GI 2612939
376	T	F	R	W	K	G	E	N	V	S	T	T	E	V	E	G	T	L	S	R	L	L	D	M	A	D	V	A	V	Y	1720440
511	T	F	R	W	R	G	E	N	V	S	T	T	E	V	E	A	V	L	S	R	L	L	G	Q	T	D	V	A	V	Y	GI 2612939

FIGURE 1C

4/12

406	G	V	E	V	P	G	T	E	G	R	A	G	M	A	A	V	A	S	P	T	G	N	C	D	L	E	R	F	A	Q	1720440
541	G	V	A	V	P	G	V	E	G	K	A	G	M	A	A	I	A	D	P	H	S	Q	L	D	P	N	S	M	Y	Q	GI 2612939
436	V	L	E	K	E	L	P	L	Y	A	R	P	I	F	L	R	L	L	P	E	L	H	K	T	G	T	Y	K	F	Q	1720440
571	E	L	Q	K	V	L	A	S	Y	A	R	P	I	F	L	R	L	L	P	Q	V	D	T	T	G	T	F	K	I	Q	GI 2612939
466	K	T	E	L	R	K	E	G	F	D	P	A	I	V	K	D	P	L	F	Y	L	D	A	Q	K	G	R	Y	V	P	1720440
601	K	T	R	L	Q	R	E	G	F	D	P	R	Q	T	S	D	R	L	F	F	L	D	L	K	Q	G	R	Y	V	P	GI 2612939
496	L	D	Q	E	A	Y	S	R	I	Q	A	G	E	E	K	L	1720440														
631	L	D	E	R	V	H	A	R	I	C	A	G	D	F	S	L	GI 2612939														

FIGURE 1D



5/12

1	M	L	V	H	L	F	R	V	G	I	R	G	G	P	F	P	G	R	L	L	P	P	L	R	F	Q	T	F	S	A	2274290	
1	M	F	S	A	L	C	R	R	G	-	-	-	-	-	F	L	T	N	K	V	S	Q	F	R	-	S	T	Y	K	C	GI 425474	
31	V	R	Y	S	D	G	Y	R	S	S	S	L	L	R	A	V	A	H	L	R	S	Q	L	W	A	H	L	P	R	A	2274290	
25	D	H	Y	N	L	K	T	H	I	K	P	L	-	K	C	S	S	S	L	R	L	T	V	G	T	G	L	-	F	I	GI 425474	
61	P	L	A	P	R	W	S	P	S	A	W	C	W	V	G	G	A	L	L	G	P	M	V	L	S	K	H	P	H	L	2274290	
53	A	L	H	S	K	I	S	P	E	S	R	I	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	Q	T	V	Q	GI 425474
91	C	L	V	A	L	C	E	A	E	E	A	-	-	P	P	A	S	S	T	P	H	V	V	G	S	R	F	N	W	K	2274290	
69	C	E	V	D	S	Y	Q	T	D	Q	I	T	F	A	K	S	G	G	I	P	R	Y	I	G	V	-	-	-	-	-	GI 425474	
119	L	F	W	Q	F	L	H	P	H	L	L	V	L	G	V	A	V	V	L	A	L	G	A	A	L	V	N	V	Q	I	2274290	
94	-	-	-	-	-	L	I	L	P	D	C	V	Y	L	F	G	A	I	L	G	A	F	V	A	A	V	M	N	V	Y	I	GI 425474
149	P	L	L	G	Q	L	V	E	V	V	A	K	Y	T	R	D	H	V	G	S	F	M	T	E	S	Q	N	L	S	2274290		
120	P	L	Y	L	G	D	F	V	S	S	L	S	R	C	V	V	T	H	E	G	-	F	V	S	A	V	Y	V	P	T	GI 425474	
179	T	H	L	L	I	L	Y	G	V	Q	G	L	L	T	F	G	Y	L	V	L	L	S	H	V	G	E	R	M	A	V	2274290	
149	L	R	L	C	S	S	Y	L	L	Q	S	L	S	T	F	L	Y	I	G	L	L	G	S	V	G	E	R	M	A	R	GI 425474	

FIGURE 2A

6/12

209	D	M	R	R	A	L	F	S	S	L	L	R	Q	D	I	T	F	F	D	A	N	K	T	G	Q	L	V	S	R	L	2274290
179	R	M	R	I	Q	L	F	R	K	L	V	Y	Q	D	V	A	Y	F	D	V	H	S	S	G	K	L	V	E	I	I	GI 425474
239	T	T	D	V	Q	E	F	K	S	S	F	K	L	V	I	S	Q	G	L	R	S	C	T	Q	V	A	G	C	L	V	2274290
209	G	S	D	V	Q	N	F	K	S	S	F	K	Q	C	I	S	Q	G	L	R	N	G	I	Q	V	V	G	S	V	F	GI 425474
269	S	L	S	M	L	S	T	R	L	T	L	L	L	M	V	A	T	P	A	L	M	G	V	G	T	L	M	G	S	G	2274290
239	A	L	L	S	I	S	P	T	L	T	A	A	L	I	G	C	L	P	C	V	F	L	I	G	S	L	M	G	T	E	GI 425474
299	L	R	K	L	S	R	Q	C	Q	E	Q	I	A	R	A	M	G	V	A	D	E	A	L	G	N	V	R	T	V	R	2274290
269	L	R	H	I	S	R	E	V	Q	S	Q	N	S	L	F	A	S	L	I	D	E	A	F	S	H	I	R	T	V	K	GI 425474
329	A	F	A	M	E	Q	R	E	E	R	Y	G	A	E	L	E	A	C	R	C	R	A	E	E	L	G	R	G	I	2274290	
299	S	L	A	M	E	D	F	L	I	N	K	I	N	Y	N	V	D	K	A	K	M	L	S	E	K	L	S	F	G	I	GI 425474
359	A	L	F	Q	G	L	S	N	I	A	F	N	C	M	V	L	G	T	L	F	I	G	G	S	L	V	A	G	Q	Q	2274290
329	G	S	F	Q	G	L	S	N	L	T	L	N	G	V	V	L	G	V	L	Y	V	G	G	H	L	M	S	R	G	E	GI 425474

FIGURE 2B

7/12

389	L	T	G	G	D	L	M	S	F	L	V	A	S	Q	T	V	Q	R	S	M	A	N	L	S	V	L	F	G	Q	V	2274290
359	L	D	A	G	H	L	M	S	F	L	A	T	T	Q	T	L	Q	R	S	L	T	Q	L	S	L	L	Y	G	Q	V	GI 425474
419	V	R	G	L	S	A	G	A	R	V	F	E	Y	M	A	L	N	P	-	-	-	C	I	P	L	S	G	G	C	-	2274290
389	V	R	G	Y	T	A	L	K	R	I	H	D	I	L	A	L	P	S	G	I	G	S	I	P	S	S	S	S	L	GI 425474	
445	C	V	P	K	E	Q	L	R	G	-	-	-	-	-	-	-	-	-	-	-	-	S	V	T	F	O	N	V	C	2274290	
419	V	V	S	K	Q	H	V	N	N	I	K	E	L	P	S	S	S	I	Y	S	A	P	S	I	E	F	S	D	V	K	GI 425474
462	F	S	Y	P	C	R	P	G	F	E	V	L	K	D	F	T	L	T	L	P	P	G	K	I	V	A	L	V	G	Q	2274290
449	F	A	Y	P	N	R	P	E	T	I	V	L	N	E	L	S	M	F	L	P	G	K	V	I	A	L	V	G	Q	GI 425474	
492	S	G	G	G	K	T	V	A	S	L	L	E	R	F	Y	D	P	T	A	G	V	V	M	L	D	G	R	D	L	2274290	
479	S	G	A	G	K	S	T	V	V	S	L	L	E	R	F	Y	D	P	I	S	G	E	I	L	L	N	G	D	K	L	GI 425474
522	R	T	L	D	P	S	W	L	R	G	Q	V	V	G	F	I	S	Q	E	P	V	L	F	G	T	I	M	E	N	2274290	
509	T	N	F	N	V	N	Y	L	R	S	K	L	I	G	Y	I	S	Q	E	P	Q	I	F	N	A	S	I	R	E	N	GI 425474

FIGURE 2C

8/12

552	I	R	F	G	K	L	E	A	S	D	E	E	V	Y	T	A	A	R	E	A	N	A	H	E	F	I	T	S	-	F	2274290
539	I	R	F	G	R	F	D	A	T	D	E	E	V	E	E	A	A	K	L	A	Y	A	H	D	F	I	S	N	D	L	GI 425474
581	P	E	G	Y	N	T	V	V	G	E	R	G	T	T	-	-	-	L	S	G	G	Q	K	Q	R	L	A	I	A	R	2274290
569	P	Y	G	Y	D	T	L	V	G	Q	G	T	G	T	I	A	G	L	S	G	G	Q	R	Q	R	I	A	I	A	R	GI 425474
608	A	L	I	K	Q	P	T	V	L	I	L	D	E	A	T	S	A	L	D	A	E	S	E	R	V	V	Q	E	A	L	2274290
599	I	L	L	K	N	A	P	I	L	L	M	D	E	A	T	S	A	L	D	T	E	S	E	A	K	V	Q	N	A	L	GI 425474
638	D	R	A	S	A	G	R	T	V	L	V	I	A	H	R	L	S	T	V	R	G	A	H	C	I	V	V	M	A	D	2274290
629	N	N	A	M	K	G	R	T	V	L	I	I	A	H	R	L	S	T	V	R	K	A	D	L	I	L	V	M	S	K	GI 425474
668	G	R	V	W	E	A	G	T	H	E	E	L	L	K	K	G	G	L	Y	A	E	L	I	R	R	Q	A	L	D	A	2274290
659	G	Q	I	V	E	K	G	T	H	S	E	L	M	A	N	H	G	Y	Y	N	L	V	Q	R	Q	-	-	-	-	-	GI 425474
698	P	R	T	A	A	P	P	P	K	K	P	E	G	P	R	S	H	Q	H	K	S	-	-	-	-	-	-	-	-	-	2274290
685	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	GI 425474

FIGURE 2D

9/12

1	M	S	V	G	V	S	T	S	A	P	L	S	P	T	S	G	T	S	V	G	M	S	T	F	S	I	M	D	Y	V	2740029
1	M	T	V	A	-	S	T	A	A	P	S	Y	T	T	S	D	T	N	R	V	I	S	T	F	S	V	V	D	Y	V	GI 3015617
31	V	F	V	L	L	V	L	S	L	A	I	G	L	Y	H	A	C	R	G	W	G	R	H	T	V	G	E	L	L	2740029	
30	V	F	G	L	L	V	L	S	L	V	I	G	L	Y	H	A	C	R	G	W	G	R	H	T	V	G	E	L	L	GI 3015617	
61	M	A	D	R	K	M	G	C	L	P	V	A	L	S	L	L	A	T	F	Q	S	A	V	A	I	L	G	V	P	S	2740029
60	M	A	D	R	K	M	G	C	L	P	V	A	L	S	L	L	A	T	F	Q	S	A	V	A	I	L	G	P	A	GI 3015617	
91	E	I	Y	R	F	G	T	Q	Y	W	F	L	G	C	C	Y	F	L	G	L	L	I	P	A	H	I	F	I	P	V	2740029
90	E	I	Y	R	F	G	T	Q	Y	W	F	L	G	C	S	Y	F	L	G	L	L	I	P	A	H	I	F	I	P	V	GI 3015617
121	F	Y	R	L	H	L	T	S	A	Y	E	Y	L	E	L	R	F	N	K	T	V	R	V	C	G	T	V	T	F	I	2740029
120	F	Y	R	L	H	L	T	S	A	Y	E	Y	L	E	L	R	F	N	K	A	V	R	I	C	G	T	V	T	F	I	GI 3015617
151	F	Q	M	V	I	Y	M	G	V	V	L	Y	A	P	S	L	A	L	N	A	V	T	G	F	D	L	W	L	S	V	2740029
150	F	Q	M	V	V	Y	M	G	V	A	L	Y	A	P	S	L	A	L	N	A	V	T	G	F	D	L	W	L	S	V	GI 3015617

FIGURE 3A

10/12

181	L	A	L	G	I	V	C	T	V	Y	T	A	L	G	G	L	K	A	V	I	W	T	D	V	F	Q	T	L	V	M	2740029
180	L	A	L	G	I	V	C	N	I	Y	T	A	L	G	G	L	K	A	V	I	W	T	D	V	F	Q	T	L	I	M	GI 3015617
211	F	L	G	Q	L	A	V	I	I	V	G	S	A	K	V	G	G	L	G	R	V	W	A	V	A	S	Q	H	G	R	2740029
210	F	L	G	Q	L	V	V	I	I	V	G	A	A	K	V	G	G	L	G	H	V	W	A	V	A	S	Q	H	G	L	GI 3015617
241	I	S	G	F	E	L	D	P	P	F	V	R	H	T	F	W	T	L	A	F	G	G	V	F	M	M	L	S	L	2740029	
240	I	S	G	I	E	L	D	P	P	F	V	R	H	T	F	W	T	L	A	F	G	G	V	F	M	M	L	S	L	GI 3015617	
271	Y	G	V	N	Q	A	Q	V	Q	R	Y	L	S	S	R	T	E	K	A	A	V	L	S	C	Y	A	V	F	P	F	2740029
270	Y	G	V	N	Q	A	Q	V	Q	R	Y	L	S	S	H	S	E	K	A	A	V	L	S	C	Y	A	V	F	P	C	GI 3015617
301	Q	Q	V	S	L	C	V	G	C	L	I	G	L	V	M	F	A	Y	Y	Q	E	Y	P	M	S	I	Q	Q	A	Q	2740029
300	Q	Q	V	A	L	C	M	S	C	L	I	G	L	V	M	F	A	Y	Y	K	K	Y	S	M	S	P	Q	Q	E	Q	GI 3015617
331	A	A	P	D	Q	F	V	L	Y	F	V	M	D	L	L	K	G	L	P	G	L	P	G	L	F	I	A	C	L	F	2740029
330	A	A	P	D	Q	L	V	L	Y	F	V	M	D	L	L	K	D	M	P	G	L	P	G	L	F	V	A	C	L	F	GI 3015617

FIGURE 3B

11/12

361	S	G	S	L	S	T	I	S	S	A	F	N	S	L	A	T	V	T	M	E	D	L	I	R	P	W	F	P	E	F	2740029	
360	S	G	S	L	S	T	I	S	S	A	F	N	S	L	A	T	V	T	M	E	D	L	I	Q	P	W	F	P	Q	L	GI 3015617	
391	S	E	A	R	A	I	M	L	S	R	G	L	A	F	G	Y	G	L	L	C	L	G	M	A	Y	I	S	S	Q	M	2740029	
390	T	E	T	R	A	I	M	L	S	R	S	L	A	F	A	Y	G	L	V	C	L	G	M	A	Y	V	S	S	H	L	GI 3015617	
421	G	P	V	L	Q	A	A	I	S	I	F	G	M	V	G	G	P	L	L	G	L	F	C	L	G	M	F	F	P	C	2740029	
420	G	S	V	L	Q	A	A	L	S	I	F	G	M	V	G	G	P	L	L	G	L	F	C	L	G	M	F	F	P	C	GI 3015617	
451	A	N	P	P	G	A	V	V	G	L	L	A	G	L	V	M	A	F	W	I	G	I	G	S	I	V	T	S	M	G	2740029	
450	A	N	P	L	G	A	I	V	G	L	L	T	G	L	T	M	A	F	W	I	G	I	G	S	I	V	S	R	M	S	GI 3015617	
481	S	S	M	P	P	S	P	S	N	G	S	S	S	F	S	L	P	T	N	L	T	V	A	T	V	T	T	L	M	P	2740029	
480	S	A	A	A	S	P	P	L	N	G	S	S	S	F	L	P	S	N	L	T	V	A	T	V	T	T	T	L	M	P	-	GI 3015617
511	T	T	F	S	K	P	T	G	L	Q	R	F	Y	S	L	S	Y	L	W	Y	S	A	H	N	S	T	T	V	I	V	2740029	
509	S	T	L	S	K	P	T	G	L	Q	Q	F	Y	S	L	S	Y	L	W	Y	S	A	H	N	S	T	T	V	I	A	GI 3015617	

FIGURE 3C

12/12

541	V	G	L	I	V	S	L	L	T	G	R	M	R	G	R	S	L	N	P	A	T	I	Y	P	V	L	P	K	L	L	2740029
539	V	G	L	I	V	S	L	L	T	G	R	M	R	G	R	S	L	N	P	G	T	I	Y	P	V	L	P	K	L	L	GI 3015617
571	S	L	L	P	L	S	C	Q	K	R	L	H	C	-	R	S	Y	G	Q	D	-	H	L	D	T	G	L	F	P	E	2740029
569	A	L	L	P	L	S	C	Q	K	R	L	-	C	W	R	S	H	N	Q	D	I	P	V	T	N	L	F	P	E	GI 3015617	
599	K	P	R	N	G	V	L	G	D	S	R	D	K	E	A	M	A	L	D	G	T	A	Y	Q	G	S	S	S	T	C	2740029
598	K	M	G	N	G	A	L	Q	D	S	R	D	K	E	R	M	A	E	D	G	L	V	H	Q	P	C	S	P	T	Y	GI 3015617
629	I	L	Q	E	T	S	L	2740029																							
628	I	V	Q	E	T	S	L	GI 3015617																							

FIGURE 3D



## SEQUENCE LISTING

<110> INCYTE PHARMACEUTICALS, INC.  
 HILLMAN, Jennifer L.  
 YUE, Henry  
 TANG, Y. Tom  
 LAL, Preeti  
 CORLEY, Neil C.  
 GUEGLER, Karl J.  
 BAUGHN, Mariah R.  
 AZIMZAI, Yalda  
 LU, Dyung Aina M.

<120> MEMBRANE TRANSPORT PROTEINS

<130> PF-0633 PCT

<140> To Be Assigned

<141> Herewith

<150> 09/186,778; unassigned; 09/200,277; unassigned; 09/221,405;  
 unassigned; 60/121,896

<151> 1998-11-04; 1998-11-04; 1998-11-24; 1998-11-24; 1998-12-22;  
 1998-12-22; 1999-02-26

<160> 43

<170> PERL Program

<210> 1

<211> 384

<212> PRT

<213> Homo sapiens

<220>

<221> misc\_feature

<223> Incyte ID No: 961344CD1

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1				5					10					15
Ser	Ser	His	Leu	Val	Ser	Arg	Thr	Gln	Asp	Ile	His	Ile	Phe	Arg
				20					25					30
Gln	Val	Thr	Ser	Arg	Gly	Glu	Ala	His	Leu	Glu	Leu	Asn	Ala	Phe
				35					40					45
Arg	Arg	Lys	His	Asp	Cys	Ala	Leu	Val	Ile	Ser	Gly	Asp	Ser	Leu
				50					55					60
Glu	Val	Cys	Leu	Lys	Tyr	Tyr	Glu	His	Glu	Phe	Val	Glu	Leu	Ala
				65					70					75
Cys	Gln	Cys	Pro	Ala	Val	Val	Cys	Cys	Arg	Cys	Ser	Pro	Thr	Gln
				80					85					90
Lys	Ala	Arg	Ile	Val	Thr	Leu	Leu	Gln	Gln	His	Thr	Gly	Arg	Arg
				95					100					105

WO 00/26245

Thr Cys Ala Ile Gly Asp Gly Gly Asn Asp Val Ser Met Ile Gln  
 110 115 120  
 Ala Ala Asp Cys Gly Ile Gly Ile Glu Gly Lys Glu Gly Lys Gln  
 125 130 135  
 Ala Ser Leu Ala Ala Asp Phe Ser Ile Thr Gln Phe Arg His Ile  
 140 145 150  
 Gly Arg Leu Leu Met Val His Gly Arg Asn Ser Tyr Lys Arg Ser  
 155 160 165  
 Ala Ala Leu Gly Gln Phe Val Met His Arg Gly Leu Ile Ile Ser  
 170 175 180  
 Thr Met Gln Ala Val Phe Ser Ser Val Phe Tyr Phe Ala Ser Val  
 185 190 195  
 Pro Leu Tyr Gln Gly Phe Leu Met Val Gly Tyr Ala Thr Ile Tyr  
 200 205 210  
 Thr Met Phe Pro Val Phe Ser Leu Val Leu Asp Gln Asp Val Lys  
 215 220 225  
 Pro Glu Met Ala Met Leu Tyr Pro Glu Leu Tyr Lys Asp Leu Thr  
 230 235 240  
 Lys Gly Arg Ser Leu Ser Phe Lys Thr Phe Leu Ile Trp Val Leu  
 245 250 255  
 Ile Ser Ile Tyr Gln Gly Gly Ile Leu Met Tyr Gly Ala Leu Val  
 260 265 270  
 Leu Phe Glu Ser Glu Phe Val His Val Val Ala Ile Ser Phe Thr  
 275 280 285  
 Ala Leu Ile Leu Thr Glu Leu Leu Met Val Ala Leu Thr Val Arg  
 290 295 300  
 Thr Trp His Trp Leu Met Val Val Ala Glu Phe Leu Ser Leu Gly  
 305 310 315  
 Cys Tyr Val Ser Ser Leu Ala Phe Leu Asn Glu Tyr Phe Gly Ile  
 320 325 330  
 Gly Arg Val Ser Phe Gly Ala Phe Leu Asp Val Ala Phe Ile Thr  
 335 340 345  
 Thr Val Thr Phe Leu Trp Lys Val Ser Ala Ile Thr Val Val Ser  
 350 355 360  
 Cys Leu Pro Leu Tyr Val Leu Lys Tyr Leu Arg Arg Lys Leu Ser  
 365 370 375  
 Pro Pro Ser Tyr Cys Lys Leu Ala Ser  
 380

&lt;210&gt; 2

&lt;211&gt; 846

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 3128782CD1

&lt;400&gt; 2

Met Pro Lys Ala Pro Lys Gln Gln Pro Pro Glu Pro Glu Trp Ile  
 1 5 10 15  
 Gly Asp Gly Glu Ser Thr Ser Pro Ser Asp Lys Val Val Lys Lys  
 20 25 30  
 Gly Lys Lys Asp Lys Lys Ile Lys Lys Thr Phe Phe Glu Glu Leu

WO 00/26245

	35	40	45
Ala Val Glu Asp Lys Gln Ala Gly Glu Glu Glu Lys Val Leu Lys			
	50	55	60
Glu Lys Glu Gln Gln Gln Gln Gln Gln Gln Gln Gln Lys			
	65	70	75
Lys Lys Arg Asp Thr Arg Lys Gly Arg Arg Lys Lys Asp Val Asp			
	80	85	90
Asp Asp Gly Glu Glu Lys Glu Leu Met Glu Arg Leu Lys Lys Leu			
	95	100	105
Ser Val Pro Thr Ser Asp Glu Glu Asp Glu Val Pro Ala Pro Lys			
	110	115	120
Pro Arg Gly Gly Lys Lys Thr Lys Gly Gly Asn Val Phe Ala Ala			
	125	130	135
Leu Ile Gln Asp Gln Ser Glu Glu Glu Glu Glu Glu Glu Lys His			
	140	145	150
Pro Pro Lys Pro Ala Lys Pro Glu Lys Asn Arg Ile Asn Lys Ala			
	155	160	165
Val Ser Glu Glu Gln Gln Pro Ala Leu Lys Gly Lys Lys Gly Lys			
	170	175	180
Glu Glu Lys Ser Lys Gly Lys Ala Lys Pro Gln Asn Lys Phe Ala			
	185	190	195
Ala Leu Asp Asn Glu Glu Glu Asp Lys Glu Glu Glu Ile Ile Lys			
	200	205	210
Glu Lys Glu Pro Pro Lys Gln Gly Lys Glu Lys Ala Lys Lys Ala			
	215	220	225
Glu Gln Gly Ser Glu Glu Glu Gly Glu Gly Glu Glu Glu Glu			
	230	235	240
Glu Gly Gly Glu Ser Lys Ala Asp Asp Pro Tyr Ala His Leu Ser			
	245	250	255
Lys Lys Glu Lys Lys Lys Leu Lys Lys Gln Met Glu Tyr Glu Arg			
	260	265	270
Gln Val Ala Ser Leu Lys Ala Ala Asn Ala Ala Glu Asn Asp Phe			
	275	280	285
Ser Val Ser Gln Ala Glu Met Ser Ser Arg Gln Ala Met Leu Glu			
	290	295	300
Asn Ala Ser Asp Ile Lys Leu Glu Lys Phe Ser Ile Ser Ala His			
	305	310	315
Gly Lys Glu Leu Phe Val Asn Ala Asp Leu Tyr Ile Val Ala Gly			
	320	325	330
Arg Arg Tyr Gly Leu Val Gly Pro Asn Gly Lys Gly Lys Thr Thr			
	335	340	345
Leu Leu Lys His Ile Ala Asn Arg Ala Leu Ser Ile Pro Pro Asn			
	350	355	360
Ile Asp Val Leu Leu Cys Glu Gln Glu Val Val Ala Asp Glu Thr			
	365	370	375
Pro Ala Val Gln Ala Val Leu Arg Ala Asp Thr Lys Arg Leu Lys			
	380	385	390
Leu Leu Glu Glu Glu Arg Arg Leu Gln Gly Gln Leu Glu Gln Gly			
	395	400	405
Asp Asp Thr Ala Ala Glu Arg Leu Glu Lys Val Tyr Glu Glu Leu			
	410	415	420
Arg Ala Thr Gly Ala Ala Ala Ala Glu Ala Lys Ala Arg Arg Ile			
	425	430	435
Leu Ala Gly Leu Gly Phe Asp Pro Glu Met Gln Asn Arg Pro Thr			
	440	445	450

WO 00/26245

Gln Lys Phe Ser Gly Gly Trp Arg Met Arg Val Ser Leu Ala Arg  
 455 460 465  
 Ala Leu Phe Met Glu Pro Thr Leu Leu Met Leu Asp Glu Pro Thr  
 470 475 480  
 Asn His Leu Asp Leu Asn Ala Val Ile Trp Leu Asn Asn Tyr Leu  
 485 490 495  
 Gln Gly Trp Arg Lys Thr Leu Leu Ile Val Ser His Asp Gln Gly  
 500 505 510  
 Phe Leu Asp Asp Val Cys Thr Asp Ile Ile His Leu Asp Ala Gln  
 515 520 525  
 Arg Leu His Tyr Tyr Arg Gly Asn Tyr Met Thr Phe Lys Lys Met  
 530 535 540  
 Tyr Gln Gln Lys Gln Lys Glu Leu Leu Lys Gln Tyr Glu Lys Gln  
 545 550 555  
 Glu Lys Lys Leu Lys Glu Leu Lys Ala Gly Gly Lys Ser Thr Lys  
 560 565 570  
 Gln Ala Glu Lys Gln Thr Lys Glu Ala Leu Thr Arg Lys Gln Gln  
 575 580 585  
 Lys Cys Arg Arg Lys Asn Gln Asp Glu Glu Ser Gln Glu Ala Pro  
 590 595 600  
 Glu Leu Leu Lys Arg Pro Lys Glu Tyr Thr Val Arg Phe Thr Phe  
 605 610 615  
 Pro Asp Pro Pro Pro Leu Ser Pro Pro Val Leu Gly Leu His Gly  
 620 625 630  
 Val Thr Phe Gly Tyr Gln Gly Gln Lys Pro Leu Phe Lys Asn Leu  
 635 640 645  
 Asp Phe Gly Ile Asp Met Asp Ser Arg Ile Cys Ile Val Gly Pro  
 650 655 660  
 Asn Gly Val Gly Lys Ser Thr Leu Leu Leu Leu Leu Thr Gly Lys  
 665 670 675  
 Leu Thr Pro Thr His Gly Glu Met Arg Lys Asn His Arg Leu Lys  
 680 685 690  
 Ile Gly Phe Phe Asn Gln Gln Tyr Ala Glu Gln Leu Arg Met Glu  
 695 700 705  
 Glu Thr Pro Thr Glu Tyr Leu Gln Arg Gly Phe Asn Leu Pro Tyr  
 710 715 720  
 Gln Asp Ala Arg Lys Cys Leu Gly Arg Phe Gly Leu Glu Ser His  
 725 730 735  
 Ala His Thr Ile Gln Ile Cys Lys Leu Ser Gly Gly Gln Lys Ala  
 740 745 750  
 Arg Val Val Phe Ala Glu Leu Ala Cys Arg Glu Pro Asp Val Leu  
 755 760 765  
 Ile Leu Asp Glu Pro Thr Asn Asn Leu Asp Ile Glu Ser Ile Asp  
 770 775 780  
 Ala Leu Gly Glu Ala Ile Asn Glu Tyr Lys Gly Ala Val Ile Val  
 785 790 795  
 Val Ser His Asp Ala Arg Leu Ile Thr Glu Thr Asn Cys Gln Leu  
 800 805 810  
 Trp Val Val Glu Glu Gln Ser Val Ser Gln Ile Asp Gly Asp Phe  
 815 820 825  
 Glu Asp Tyr Lys Arg Glu Val Leu Glu Ala Leu Gly Glu Val Met  
 830 835 840  
 Val Ser Arg Pro Arg Glu  
 845

WO 00/26245

<210> 3  
 <211> 511  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <223> Incyte ID No: 1720440CD1

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 1 5 10 15  
 Lys Leu Gly Val Glu Ala Ala Leu Ile Asn Thr Asn Leu Arg Arg  
 20 25 30  
 Asp Ala Leu Leu His Cys Leu Thr Thr Ser Arg Ala Arg Ala Leu  
 35 40 45  
 Val Phe Gly Ser Glu Met Ala Ser Ala Ile Cys Glu Val His Ala  
 50 55 60  
 Ser Leu Asp Pro Ser Leu Ser Leu Phe Cys Ser Gly Ser Trp Glu  
 65 70 75  
 Pro Gly Ala Val Pro Pro Ser Thr Glu His Leu Asp Pro Leu Leu  
 80 85 90  
 Lys Asp Ala Pro Lys His Leu Pro Ser Cys Pro Asp Lys Gly Phe  
 95 100 105  
 Thr Asp Lys Leu Phe Tyr Ile Tyr Thr Ser Gly Thr Thr Gly Leu  
 110 115 120  
 Pro Lys Ala Ala Ile Val Val His Ser Arg Tyr Tyr Arg Met Ala  
 125 130 135  
 Ala Leu Val Tyr Tyr Gly Phe Arg Met Arg Pro Asn Asp Ile Val  
 140 145 150  
 Tyr Asp Cys Leu Pro Leu Tyr His Ser Ala Gly Asn Ile Val Gly  
 155 160 165  
 Ile Gly Gln Cys Leu Leu His Gly Met Thr Val Val Ile Arg Lys  
 170 175 180  
 Lys Phe Ser Ala Ser Arg Phe Trp Asp Asp Cys Ile Lys Tyr Asn  
 185 190 195  
 Cys Thr Ile Val Gln Tyr Ile Gly Glu Leu Cys Arg Tyr Leu Leu  
 200 205 210  
 Asn Gln Pro Pro Arg Glu Ala Glu Asn Gln His Gln Val Arg Met  
 215 220 225  
 Ala Leu Gly Asn Gly Leu Arg Gln Ser Ile Trp Thr Asn Phe Ser  
 230 235 240  
 Ser Arg Phe His Ile Pro Gln Val Ala Glu Phe Tyr Gly Ala Thr  
 245 250 255  
 Glu Cys Asn Cys Ser Leu Gly Asn Phe Asp Ser Gln Val Gly Ala  
 260 265 270  
 Cys Gly Phe Asn Ser Arg Ile Leu Ser Ser Val Tyr Pro Ile Arg  
 275 280 285  
 Leu Val Arg Val Asn Glu Asp Thr Met Glu Leu Ile Arg Gly Pro  
 290 295 300  
 Asp Gly Val Cys Ile Pro Cys Gln Pro Gly Glu Pro Gly Gln Leu  
 305 310 315  
 Val Gly Arg Ile Ile Gln Lys Asp Pro Leu Arg Arg Phe Asp Gly  
 320 325 330  
 Tyr Leu Asn Gln Gly Ala Asn Asn Lys Lys Ile Ala Lys Asp Val

WO 00/26245

	335	340	345
Phe Lys Lys Gly Asp Gln Ala Tyr Leu		Thr Gly Asp Val Leu Val	
	350	355	360
Met Asp Glu Leu Gly Tyr Leu Tyr Phe		Arg Asp Arg Thr Gly Asp	
	365	370	375
Thr Phe Arg Trp Lys Gly Glu Asn Val		Ser Thr Thr Glu Val Glu	
	380	385	390
Gly Thr Leu Ser Arg Leu Leu Asp Met		Ala Asp Val Ala Val Tyr	
	395	400	405
Gly Val Glu Val Pro Gly Thr Glu Gly		Arg Ala Gly Met Ala Ala	
	410	415	420
Val Ala Ser Pro Thr Gly Asn Cys Asp		Leu Glu Arg Phe Ala Gln	
	425	430	435
Val Leu Glu Lys Glu Leu Pro Leu Tyr		Ala Arg Pro Ile Phe Leu	
	440	445	450
Arg Leu Leu Pro Glu Leu His Lys Thr		Gly Thr Tyr Lys Phe Gln	
	455	460	465
Lys Thr Glu Leu Arg Lys Glu Gly Phe		Asp Pro Ala Ile Val Lys	
	470	475	480
Asp Pro Leu Phe Tyr Leu Asp Ala Gln		Lys Gly Arg Tyr Val Pro	
	485	490	495
Leu Asp Gln Glu Ala Tyr Ser Arg Ile		Gln Ala Gly Glu Glu Lys	
	500	505	510

Leu

<210> 4  
 <211> 718  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <223> Incyte ID No: 2274290CD1

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 Met Leu Val His Leu Phe Arg Val Gly Ile Arg Gly Gly Pro Phe  
 1 5 10 15  
 Pro Gly Arg Leu Leu Pro Pro Leu Arg Phe Gln Thr Phe Ser Ala  
 20 25 30  
 Val Arg Tyr Ser Asp Gly Tyr Arg Ser Ser Ser Leu Leu Arg Ala  
 35 40 45  
 Val Ala His Leu Arg Ser Gln Leu Trp Ala His Leu Pro Arg Ala  
 50 55 60  
 Pro Leu Ala Pro Arg Trp Ser Pro Ser Ala Trp Cys Trp Val Gly  
 65 70 75  
 Gly Ala Leu Leu Gly Pro Met Val Leu Ser Lys His Pro His Leu  
 80 85 90  
 Cys Leu Val Ala Leu Cys Glu Ala Glu Glu Ala Pro Pro Ala Ser  
 95 100 105  
 Ser Thr Pro His Val Val Gly Ser Arg Phe Asn Trp Lys Leu Phe  
 110 115 120  
 Trp Gln Phe Leu His Pro His Leu Leu Val Leu Gly Val Ala Val  
 125 130 135  
 Val Leu Ala Leu Gly Ala Ala Leu Val Asn Val Gln Ile Pro Leu

WO 00/26245

	140	145	150
Leu Leu Gly Gln Leu Val Glu Val Val	Ala Lys Tyr Thr Arg Asp		
	155	160	165
His Val Gly Ser Phe Met Thr Glu Ser	Gln Asn Leu Ser Thr His		
	170	175	180
Leu Leu Ile Leu Tyr Gly Val Gln Gly	Leu Leu Thr Phe Gly Tyr		
	185	190	195
Leu Val Leu Leu Ser His Val Gly Glu	Arg Met Ala Val Asp Met		
	200	205	210
Arg Arg Ala Leu Phe Ser Ser Leu Leu	Arg Gln Asp Ile Thr Phe		
	215	220	225
Phe Asp Ala Asn Lys Thr Gly Gln Leu	Val Ser Arg Leu Thr Thr		
	230	235	240
Asp Val Gln Glu Phe Lys Ser Ser Phe	Lys Leu Val Ile Ser Gln		
	245	250	255
Gly Leu Arg Ser Cys Thr Gln Val Ala	Gly Cys Leu Val Ser Leu		
	260	265	270
Ser Met Leu Ser Thr Arg Leu Thr Leu	Leu Leu Met Val Ala Thr		
	275	280	285
Pro Ala Leu Met Gly Val Gly Thr Leu	Met Gly Ser Gly Leu Arg		
	290	295	300
Lys Leu Ser Arg Gln Cys Gln Glu Gln	Ile Ala Arg Ala Met Gly		
	305	310	315
Val Ala Asp Glu Ala Leu Gly Asn Val	Arg Thr Val Arg Ala Phe		
	320	325	330
Ala Met Glu Gln Arg Glu Glu Glu Arg	Tyr Gly Ala Glu Leu Glu		
	335	340	345
Ala Cys Arg Cys Arg Ala Glu Glu Leu	Gly Arg Gly Ile Ala Leu		
	350	355	360
Phe Gln Gly Leu Ser Asn Ile Ala Phe	Asn Cys Met Val Leu Gly		
	365	370	375
Thr Leu Phe Ile Gly Gly Ser Leu Val	Ala Gly Gln Gln Leu Thr		
	380	385	390
Gly Gly Asp Leu Met Ser Phe Leu Val	Ala Ser Gln Thr Val Gln		
	395	400	405
Arg Ser Met Ala Asn Leu Ser Val Leu	Phe Gly Gln Val Val Arg		
	410	415	420
Gly Leu Ser Ala Gly Ala Arg Val Phe	Glu Tyr Met Ala Leu Asn		
	425	430	435
Pro Cys Ile Pro Leu Ser Gly Gly Cys	Cys Val Pro Lys Glu Gln		
	440	445	450
Leu Arg Gly Ser Val Thr Phe Gln Asn	Val Cys Phe Ser Tyr Pro		
	455	460	465
Cys Arg Pro Gly Phe Glu Val Leu Lys	Asp Phe Thr Leu Thr Leu		
	470	475	480
Pro Pro Gly Lys Ile Val Ala Leu Val	Gly Gln Ser Gly Gly Gly		
	485	490	495
Lys Thr Thr Val Ala Ser Leu Leu Glu	Arg Phe Tyr Asp Pro Thr		
	500	505	510
Ala Gly Val Val Met Leu Asp Gly Arg	Asp Leu Arg Thr Leu Asp		
	515	520	525
Pro Ser Trp Leu Arg Gly Gln Val Val	Gly Phe Ile Ser Gln Glu		
	530	535	540
Pro Val Leu Phe Gly Thr Thr Ile Met	Glu Asn Ile Arg Phe Gly		
	545	550	555

WO 00/26245

Lys Leu Glu Ala Ser Asp Glu Glu Val Tyr Thr Ala Ala Arg Glu  
 560 565 570  
 Ala Asn Ala His Glu Phe Ile Thr Ser Phe Pro Glu Gly Tyr Asn  
 575 580 585  
 Thr Val Val Gly Glu Arg Gly Thr Thr Leu Ser Gly Gly Gln Lys  
 590 595 600  
 Gln Arg Leu Ala Ile Ala Arg Ala Leu Ile Lys Gln Pro Thr Val  
 605 610 615  
 Leu Ile Leu Asp Glu Ala Thr Ser Ala Leu Asp Ala Glu Ser Glu  
 620 625 630  
 Arg Val Val Gln Glu Ala Leu Asp Arg Ala Ser Ala Gly Arg Thr  
 635 640 645  
 Val Leu Val Ile Ala His Arg Leu Ser Thr Val Arg Gly Ala His  
 650 655 660  
 Cys Ile Val Val Met Ala Asp Gly Arg Val Trp Glu Ala Gly Thr  
 665 670 675  
 His Glu Glu Leu Leu Lys Lys Gly Gly Leu Tyr Ala Glu Leu Ile  
 680 685 690  
 Arg Arg Gln Ala Leu Asp Ala Pro Arg Thr Ala Ala Pro Pro Pro  
 695 700 705  
 Lys Lys Pro Glu Gly Pro Arg Ser His Gln His Lys Ser  
 710 715

&lt;210&gt; 5

&lt;211&gt; 635

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 2740029CD1

&lt;400&gt; 5

Met Ser Val Gly Val Ser Thr Ser Ala Pro Leu Ser Pro Thr Ser  
 1 5 10 15  
 Gly Thr Ser Val Gly Met Ser Thr Phe Ser Ile Met Asp Tyr Val  
 20 25 30  
 Val Phe Val Leu Leu Leu Val Leu Ser Leu Ala Ile Gly Leu Tyr  
 35 40 45  
 His Ala Cys Arg Gly Trp Gly Arg His Thr Val Gly Glu Leu Leu  
 50 55 60  
 Met Ala Asp Arg Lys Met Gly Cys Leu Pro Val Ala Leu Ser Leu  
 65 70 75  
 Leu Ala Thr Phe Gln Ser Ala Val Ala Ile Leu Gly Val Pro Ser  
 80 85 90  
 Glu Ile Tyr Arg Phe Gly Thr Gln Tyr Trp Phe Leu Gly Cys Cys  
 95 100 105  
 Tyr Phe Leu Gly Leu Leu Ile Pro Ala His Ile Phe Ile Pro Val  
 110 115 120  
 Phe Tyr Arg Leu His Leu Thr Ser Ala Tyr Glu Tyr Leu Glu Leu  
 125 130 135  
 Arg Phe Asn Lys Thr Val Arg Val Cys Gly Thr Val Thr Phe Ile  
 140 145 150  
 Phe Gln Met Val Ile Tyr Met Gly Val Val Leu Tyr Ala Pro Ser



WO 00/26245

155	160	165
Leu Ala Leu Asn Ala Val Thr Gly Phe Asp Leu Trp Leu Ser Val		
170	175	180
Leu Ala Leu Gly Ile Val Cys Thr Val Tyr Thr Ala Leu Gly Gly		
185	190	195
Leu Lys Ala Val Ile Trp Thr Asp Val Phe Gln Thr Leu Val Met		
200	205	210
Phe Leu Gly Gln Leu Ala Val Ile Ile Val Gly Ser Ala Lys Val		
215	220	225
Gly Gly Leu Gly Arg Val Trp Ala Val Ala Ser Gln His Gly Arg		
230	235	240
Ile Ser Gly Phe Glu Leu Asp Pro Asp Pro Phe Val Arg His Thr		
245	250	255
Phe Trp Thr Leu Ala Phe Gly Gly Val Phe Met Met Leu Ser Leu		
260	265	270
Tyr Gly Val Asn Gln Ala Gln Val Gln Arg Tyr Leu Ser Ser Arg		
275	280	285
Thr Glu Lys Ala Ala Val Leu Ser Cys Tyr Ala Val Phe Pro Phe		
290	295	300
Gln Gln Val Ser Leu Cys Val Gly Cys Leu Ile Gly Leu Val Met		
305	310	315
Phe Ala Tyr Tyr Gln Glu Tyr Pro Met Ser Ile Gln Gln Ala Gln		
320	325	330
Ala Ala Pro Asp Gln Phe Val Leu Tyr Phe Val Met Asp Leu Leu		
335	340	345
Lys Gly Leu Pro Gly Leu Pro Gly Leu Phe Ile Ala Cys Leu Phe		
350	355	360
Ser Gly Ser Leu Ser Thr Ile Ser Ser Ala Phe Asn Ser Leu Ala		
365	370	375
Thr Val Thr Met Glu Asp Leu Ile Arg Pro Trp Phe Pro Glu Phe		
380	385	390
Ser Glu Ala Arg Ala Ile Met Leu Ser Arg Gly Leu Ala Phe Gly		
395	400	405
Tyr Gly Leu Leu Cys Leu Gly Met Ala Tyr Ile Ser Ser Gln Met		
410	415	420
Gly Pro Val Leu Gln Ala Ala Ile Ser Ile Phe Gly Met Val Gly		
425	430	435
Gly Pro Leu Leu Gly Leu Phe Cys Leu Gly Met Phe Phe Pro Cys		
440	445	450
Ala Asn Pro Pro Gly Ala Val Val Gly Leu Leu Ala Gly Leu Val		
455	460	465
Met Ala Phe Trp Ile Gly Ile Gly Ser Ile Val Thr Ser Met Gly		
470	475	480
Ser Ser Met Pro Pro Ser Pro Ser Asn Gly Ser Ser Phe Ser Leu		
485	490	495
Pro Thr Asn Leu Thr Val Ala Thr Val Thr Thr Leu Met Pro Leu		
500	505	510
Thr Thr Phe Ser Lys Pro Thr Gly Leu Gln Arg Phe Tyr Ser Leu		
515	520	525
Ser Tyr Leu Trp Tyr Ser Ala His Asn Ser Thr Thr Val Ile Val		
530	535	540
Val Gly Leu Ile Val Ser Leu Leu Thr Gly Arg Met Arg Gly Arg		
545	550	555
Ser Leu Asn Pro Ala Thr Ile Tyr Pro Val Leu Pro Lys Leu Leu		
560	565	570

Ser Leu Leu Pro Leu Ser Cys Gln Lys Arg Leu His Cys Arg Ser  
 575 580 585  
 Tyr Gly Gln Asp His Leu Asp Thr Gly Leu Phe Pro Glu Lys Pro  
 590 595 600  
 Arg Asn Gly Val Leu Gly Asp Ser Arg Asp Lys Glu Ala Met Ala  
 605 610 615  
 Leu Asp Gly Thr Ala Tyr Gln Gly Ser Ser Ser Thr Cys Ile Leu  
 620 625 630  
 Gln Glu Thr Ser Leu  
 635

&lt;210&gt; 6

&lt;211&gt; 535

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 2414415CD1

&lt;400&gt; 6

Met Glu Glu Gly Ala Arg His Arg Asn Asn Thr Glu Lys Lys His  
 1 5 10 15  
 Pro Gly Gly Gly Glu Ser Asp Ala Ser Pro Glu Ala Gly Ser Gly  
 20 25 30  
 Gly Gly Gly Val Ala Leu Lys Lys Glu Ile Gly Leu Val Ser Ala  
 35 40 45  
 Cys Gly Ile Ile Val Gly Asn Ile Ile Gly Ser Gly Ile Phe Val  
 50 55 60  
 Ser Pro Lys Gly Val Leu Glu Asn Ala Gly Ser Val Gly Leu Ala  
 65 70 75  
 Leu Ile Val Trp Ile Val Thr Gly Phe Ile Thr Val Val Gly Ala  
 80 85 90  
 Leu Cys Tyr Ala Glu Leu Gly Val Thr Ile Pro Lys Ser Gly Gly  
 95 100 105  
 Asp Tyr Ser Tyr Val Lys Asp Ile Phe Gly Gly Leu Ala Gly Phe  
 110 115 120  
 Leu Arg Leu Trp Ile Ala Val Leu Val Ile Tyr Pro Thr Asn Gln  
 125 130 135  
 Ala Val Ile Ala Leu Thr Phe Ser Asn Tyr Val Leu Gln Pro Leu  
 140 145 150  
 Phe Pro Thr Cys Phe Pro Pro Glu Ser Gly Leu Arg Leu Leu Ala  
 155 160 165  
 Ala Ile Cys Leu Leu Leu Leu Thr Trp Val Asn Cys Ser Ser Val  
 170 175 180  
 Arg Trp Ala Thr Arg Val Gln Asp Ile Phe Thr Ala Gly Lys Leu  
 185 190 195  
 Leu Ala Leu Ala Leu Ile Ile Ile Met Gly Ile Val Gln Ile Cys  
 200 205 210  
 Lys Gly Glu Tyr Phe Trp Leu Glu Pro Lys Asn Ala Phe Glu Asn  
 215 220 225  
 Phe Gln Glu Pro Asp Ile Gly Leu Val Ala Leu Ala Phe Leu Gln  
 230 235 240  
 Gly Ser Phe Ala Tyr Gly Gly Trp Asn Phe Leu Asn Tyr Val Thr

WO 00/26245

	245	250	255
Glu Glu Leu Val Asp Pro Tyr Lys Asn Leu Pro Arg Ala Ile Phe			270
	260	265	
Ile Ser Ile Pro Leu Val Thr Phe Val Tyr Val Phe Ala Asn Val			285
	275	280	
Ala Tyr Val Thr Ala Met Ser Pro Gln Glu Leu Leu Ala Ser Asn			300
	290	295	
Ala Val Ala Val Thr Phe Gly Glu Lys Leu Leu Gly Val Met Ala			315
	305	310	
Trp Ile Met Pro Ile Ser Val Ala Leu Ser Thr Phe Gly Gly Val			330
	320	325	
Asn Gly Ser Leu Phe Thr Ser Ser Arg Leu Phe Phe Ala Gly Ala			345
	335	340	
Arg Glu Gly His Leu Pro Ser Val Leu Ala Met Ile His Val Lys			360
	350	355	
Arg Cys Thr Pro Ile Pro Ala Leu Leu Phe Thr Cys Ile Ser Thr			375
	365	370	
Leu Leu Met Leu Val Thr Ser Asp Met Tyr Thr Leu Ile Asn Tyr			390
	380	385	
Val Gly Phe Ile Asn Tyr Leu Phe Tyr Gly Val Thr Val Ala Gly			405
	395	400	
Gln Ile Val Leu Arg Trp Lys Lys Pro Asp Ile Pro Arg Pro Ile			420
	410	415	
Lys Ile Asn Leu Leu Phe Pro Ile Ile Tyr Leu Leu Phe Trp Ala			435
	425	430	
Phe Leu Leu Val Phe Ser Leu Trp Ser Glu Pro Val Val Cys Gly			450
	440	445	
Ile Gly Leu Ala Ile Met Leu Thr Gly Val Pro Val Tyr Phe Leu			465
	455	460	
Gly Val Tyr Trp Gln His Lys Pro Lys Cys Phe Ser Asp Phe Ile			480
	470	475	
Glu Leu Leu Thr Leu Val Ser Gln Lys Met Cys Val Val Val Tyr			495
	485	490	
Pro Glu Val Glu Arg Gly Ser Gly Thr Glu Glu Ala Asn Glu Asp			510
	500	505	
Met Glu Glu Gln Gln Gln Pro Met Tyr Gln Pro Thr Pro Thr Lys			525
	515	520	
Asp Lys Asp Val Ala Gly Gln Pro Gln Pro			
	530	535	

&lt;210&gt; 7

&lt;211&gt; 456

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 2466714CD1

&lt;400&gt; 7

Met Glu Ala Ser Trp Gly Ser Phe Asn Ala Glu Arg Gly Trp Tyr			
	5	10	15
1			
Val Ser Val Gln Gln Pro Glu Glu Ala Glu Ala Glu Glu Leu Ser			
	20	25	30

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Pro Leu Leu Ser Asn Glu Leu His Arg Gln Arg Ser Pro Gly Val  
 35 40 45  
 Ser Phe Gly Leu Ser Val Phe Asn Leu Met Asn Ala Ile Met Gly  
 50 55 60  
 Ser Gly Ile Leu Gly Leu Ala Tyr Val Met Ala Asn Thr Gly Val  
 65 70 75  
 Phe Gly Phe Ser Phe Leu Leu Leu Thr Val Ala Leu Leu Ala Ser  
 80 85 90  
 Tyr Ser Val His Leu Leu Leu Ser Met Cys Ile Gln Thr Ala Val  
 95 100 105  
 Thr Ser Tyr Glu Asp Leu Gly Leu Phe Ala Phe Gly Leu Pro Gly  
 110 115 120  
 Lys Leu Val Val Ala Gly Thr Ile Ile Ile Gln Asn Ile Gly Ala  
 125 130 135  
 Met Ser Ser Tyr Leu Leu Ile Ile Lys Thr Glu Leu Pro Ala Ala  
 140 145 150  
 Ile Ala Glu Phe Leu Thr Gly Asp Tyr Asn Arg Tyr Trp Tyr Leu  
 155 160 165  
 Asp Gly Gln Thr Leu Leu Ile Ile Ile Cys Val Gly Ile Val Phe  
 170 175 180  
 Pro Leu Ala Leu Leu Pro Lys Ile Gly Phe Leu Gly Tyr Thr Ser  
 185 190 195  
 Ser Leu Ser Phe Phe Phe Met Met Phe Phe Ala Leu Val Val Ile  
 200 205 210  
 Ile Lys Lys Trp Ser Ile Pro Cys Pro Leu Thr Leu Asn Tyr Val  
 215 220 225  
 Glu Lys Gly Phe Gln Ile Ser Asn Val Thr Asp Asp Cys Lys Pro  
 230 235 240  
 Lys Leu Phe His Phe Ser Lys Glu Ser Ala Tyr Ala Leu Pro Thr  
 245 250 255  
 Met Ala Phe Ser Phe Leu Cys His Thr Ser Ile Leu Pro Ile Tyr  
 260 265 270  
 Cys Glu Leu Gln Ser Pro Ser Lys Lys Arg Met Gln Asn Val Thr  
 275 280 285  
 Asn Thr Ala Ile Ala Leu Ser Phe Leu Ile Tyr Phe Ile Ser Ala  
 290 295 300  
 Leu Phe Gly Tyr Leu Thr Phe Tyr Asp Lys Val Glu Ser Glu Leu  
 305 310 315  
 Leu Lys Gly Tyr Ser Lys Tyr Leu Ser His Asp Val Val Val Met  
 320 325 330  
 Thr Val Lys Leu Cys Ile Leu Phe Ala Val Leu Leu Thr Val Pro  
 335 340 345  
 Leu Ile His Phe Pro Ala Arg Lys Ala Val Thr Met Met Phe Phe  
 350 355 360  
 Ser Asn Phe Pro Phe Ser Trp Ile Arg His Phe Leu Ile Thr Leu  
 365 370 375  
 Ala Leu Asn Ile Ile Ile Val Leu Leu Ala Ile Tyr Val Pro Asp  
 380 385 390  
 Ile Arg Asn Val Phe Gly Val Val Gly Ala Ser Thr Ser Thr Cys  
 395 400 405  
 Leu Ile Phe Ile Phe Pro Gly Leu Phe Tyr Leu Lys Leu Ser Arg  
 410 415 420  
 Glu Asp Phe Leu Ser Trp Lys Lys Leu Gly Ala Phe Val Leu Leu  
 425 430 435  
 Ile Phe Gly Ile Leu Val Gly Asn Phe Ser Leu Ala Leu Ile Ile

440  
Phe Asp Trp Ile Asn Lys  
455

445

450

<210> 8  
<211> 325  
<212> PRT  
<213> Homo sapiens

<220>  
<221> misc\_feature  
<223> Incyte ID No: 2617942CD1

<400> 8  
Met Phe Ala Asn Leu Lys Tyr Val Ser Leu Gly Ile Leu Val Phe  
1 5 10 15  
Gln Thr Thr Ser Leu Val Leu Thr Met Arg Tyr Ser Arg Thr Leu  
20 25 30  
Lys Glu Glu Gly Pro Arg Tyr Leu Ser Ser Thr Ala Val Val Val  
35 40 45  
Ala Glu Leu Leu Lys Ile Met Ala Cys Ile Leu Leu Val Tyr Lys  
50 55 60  
Asp Ser Lys Cys Ser Leu Arg Ala Leu Asn Arg Val Leu His Asp  
65 70 75  
Glu Ile Leu Asn Lys Pro Met Glu Thr Leu Lys Leu Ala Ile Pro  
80 85 90  
Ser Gly Ile Tyr Thr Leu Gln Asn Asn Leu Leu Tyr Val Ala Leu  
95 100 105  
Ser Asn Leu Asp Ala Ala Thr Tyr Gln Val Thr Tyr Gln Leu Lys  
110 115 120  
Ile Leu Thr Thr Ala Leu Phe Ser Val Ser Met Leu Ser Lys Lys  
125 130 135  
Leu Gly Val Tyr Gln Trp Leu Ser Leu Val Ile Leu Met Thr Gly  
140 145 150  
Val Ala Phe Val Gln Trp Pro Ser Asp Ser Gln Leu Asp Ser Lys  
155 160 165  
Glu Leu Ser Ala Gly Ser Gln Phe Val Gly Leu Met Ala Val Leu  
170 175 180  
Thr Ala Cys Phe Ser Ser Gly Phe Ala Gly Val Tyr Phe Glu Lys  
185 190 195  
Ile Leu Lys Glu Thr Lys Gln Ser Val Trp Ile Arg Asn Ile Gln  
200 205 210  
Leu Gly Phe Phe Gly Ser Ile Phe Gly Leu Met Gly Val Tyr Ile  
215 220 225  
Tyr Asp Gly Glu Leu Val Ser Lys Asn Gly Phe Phe Gln Gly Tyr  
230 235 240  
Asn Arg Leu Thr Trp Ile Val Val Val Leu Gln Ala Leu Gly Gly  
245 250 255  
Leu Val Ile Ala Ala Val Ile Lys Tyr Ala Asp Asn Ile Leu Lys  
260 265 270  
Gly Phe Ala Thr Ser Leu Ser Ile Ile Leu Ser Thr Leu Ile Ser  
275 280 285  
Tyr Phe Trp Leu Gln Asp Phe Val Pro Thr Ser Val Phe Phe Leu  
290 295 300

```
<210> 9
<211> 178
<212> PRT
<213> Homo sapiens
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<400>	9
Met Ser Leu Ser Pro Arg Ser Gln Leu Ala Ile Ile Pro Gln Glu	15
1 5 10	
Pro Phe Leu Phe Ser Gly Thr Val Arg Glu Asn Leu Asp Pro Gln	30
20 25	
Gly Leu His Lys Asp Arg Ala Leu Trp Gln Ala Leu Lys Gln Cys	45
35 40	
His Leu Ser Glu Val Ile Thr Ser Met Gly Gly Leu Asp Gly Glu	60
50 55	
Leu Gly Glu Gly Gly Arg Ser Leu Ser Leu Gly Gln Arg Gln Leu	75
65 70	
Leu Cys Leu Ala Arg Ala Leu Leu Thr Asp Ala Lys Ile Leu Cys	90
80 85	
Ile Asp Glu Ala Thr Ala Ser Val Asp Gln Lys Thr Asp Gln Leu	105
95 100	
Leu Gln Gln Thr Ile Cys Lys Arg Phe Ala Asn Lys Thr Val Leu	120
110 115	
Thr Ile Ala His Arg Leu Asn Thr Ile Leu Asn Ser Asp Arg Val	135
125 130	
Leu Val Leu Gln Ala Gly Arg Val Val Glu Leu Asp Ser Pro Ala	150
140 145	
Thr Leu Arg Asn Gln Pro His Ser Leu Phe Gln Gln Leu Leu Gln	165
155 160	
Ser Ser Gln Gln Gly Val Pro Ala Ser Leu Gly Gly Pro	175
170	

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<210> 10
<211> 255
<212> PRT
<213> Homo sapiens
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<220>
<221> misc_feature
<223> Incyte ID No: 4074113CD1
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<400> 10
Met Glu Arg Glu Met Glu Gly Arg Pro Leu His Asn Glu Gly Trp
  1             5             10             15
Ile Asp Arg Ser Arg Val Gln Gln Lys Asp Leu Pro Asn Lys Cys

```

	20	25	30
Pro Gln Thr Leu Trp Ser Glu Gln Ala Phe Pro Pro Asn Pro Gly			
	35	40	45
Gln Val Gly Ile Val Gly Arg Thr Gly Ala Gly Lys Ser Ser Leu			
	50	55	60
Ala Ser Gly Leu Leu Arg Leu Pro Glu Ala Ala Glu Gly Gly Ile			
	65	70	75
Trp Ile Asp Gly Val Pro Ile Ala His Val Gly Leu His Thr Leu			
	80	85	90
Arg Ser Arg Ile Ser Ile Ile Pro Gln Asp Pro Ile Leu Phe Pro			
	95	100	105
Gly Ser Leu Arg Met Asn Leu Asp Leu Leu Gln Glu His Ser Asp			
	110	115	120
Glu Ala Ile Trp Ala Ala Leu Glu Thr Val Gln Leu Lys Ala Leu			
	125	130	135
Val Ala Ser Leu Pro Gly Gln Leu Gln Tyr Lys Cys Ala Asp Arg			
	140	145	150
Gly Glu Asp Leu Ser Val Gly Gln Lys Gln Leu Leu Cys Leu Ala			
	155	160	165
Arg Ala Leu Leu Arg Lys Thr Gln Ile Leu Ile Leu Asp Glu Ala			
	170	175	180
Thr Ala Ala Val Asp Pro Gly Thr Glu Leu Gln Met Gln Ala Met			
	185	190	195
Leu Gly Ser Trp Phe Ala Gln Cys Thr Val Leu Leu Ile Ala His			
	200	205	210
Arg Leu Arg Ser Val Met Asp Cys Ala Arg Val Leu Val Met Asp			
	215	220	225
Lys Gly Gln Val Ala Glu Ser Gly Ser Pro Ala Gln Leu Leu Ala			
	230	235	240
Gln Lys Gly Leu Phe Tyr Arg Leu Ala Gln Glu Ser Gly Leu Val			
	245	250	255

&lt;210&gt; 11

&lt;211&gt; 462

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 1413743CD1

&lt;400&gt; 11

Met Ala Gln Val Ser Ile Asn Asn Asp Tyr Ser Glu Trp Asp Leu		
1	5	10
		15
Ser Thr Asp Ala Gly Glu Arg Ala Arg Leu Leu Gln Ser Pro Cys		
	20	25
		30
Val Asp Thr Ala Pro Lys Ser Glu Trp Glu Ala Ser Pro Gly Gly		
	35	40
		45
Leu Asp Arg Gly Thr Thr Ser Thr Leu Gly Ala Ile Phe Ile Val		
	50	55
		60
Val Asn Ala Cys Leu Gly Ala Gly Leu Leu Asn Phe Pro Ala Ala		
	65	70
		75
Phe Ser Thr Ala Gly Gly Val Ala Ala Gly Ile Ala Leu Gln Met		
	80	85
		90

Gly Met Leu Val Phe Ile Ile Ser Gly Leu Val Ile Leu Ala Tyr  
 95 100 105  
 Cys Ser Gln Ala Ser Asn Glu Arg Thr Tyr Gln Glu Val Val Trp  
 110 115 120  
 Ala Val Cys Gly Lys Leu Thr Gly Val Leu Cys Glu Val Ala Ile  
 125 130 135  
 Ala Val Tyr Thr Phe Gly Thr Cys Ile Ala Phe Leu Ile Ile Ile  
 140 145 150  
 Gly Asp Gln Gln Asp Lys Ile Ile Ala Val Met Ala Lys Glu Pro  
 155 160 165  
 Glu Gly Ala Ser Gly Pro Trp Tyr Thr Asp Arg Lys Phe Thr Ile  
 170 175 180  
 Ser Leu Thr Ala Phe Leu Phe Ile Leu Pro Leu Ser Ile Pro Arg  
 185 190 195  
 Glu Ile Gly Phe Gln Lys Tyr Ala Ser Phe Leu Ser Val Val Gly  
 200 205 210  
 Thr Trp Tyr Val Thr Ala Ile Val Ile Ile Lys Tyr Ile Trp Pro  
 215 220 225  
 Asp Lys Glu Met Thr Pro Gly Asn Ile Leu Thr Arg Pro Ala Ser  
 230 235 240  
 Trp Met Ala Val Phe Asn Ala Met Pro Thr Ile Cys Phe Gly Phe  
 245 250 255  
 Gln Cys His Val Ser Ser Val Pro Val Phe Asn Ser Met Gln Gln  
 260 265 270  
 Pro Glu Val Lys Thr Trp Gly Gly Val Val Thr Ala Ala Met Val  
 275 280 285  
 Ile Ala Leu Ala Val Tyr Met Gly Thr Gly Ile Cys Gly Phe Leu  
 290 295 300  
 Thr Phe Gly Ala Ala Val Asp Pro Asp Val Leu Leu Ser Tyr Pro  
 305 310 315  
 Ser Glu Asp Met Ala Val Ala Val Ala Arg Ala Phe Ile Ile Leu  
 320 325 330  
 Ser Val Leu Thr Ser Tyr Pro Ile Leu His Phe Cys Gly Arg Ala  
 335 340 345  
 Val Val Glu Gly Leu Trp Leu Arg Tyr Gln Gly Val Pro Val Glu  
 350 355 360  
 Glu Asp Val Gly Arg Glu Arg Arg Arg Arg Val Leu Gln Thr Leu  
 365 370 375  
 Val Trp Phe Leu Leu Thr Leu Leu Leu Ala Leu Phe Ile Pro Asp  
 380 385 390  
 Ile Gly Lys Val Ile Ser Val Ile Gly Gly Leu Ala Ala Cys Phe  
 395 400 405  
 Ile Phe Val Phe Pro Gly Leu Cys Leu Ile Gln Ala Lys Leu Ser  
 410 415 420  
 Glu Met Glu Glu Val Lys Pro Ala Ser Trp Trp Val Leu Val Ser  
 425 430 435  
 Tyr Gly Val Leu Leu Val Thr Leu Gly Ala Phe Ile Phe Gly Gln  
 440 445 450  
 Thr Thr Ala Asn Ala Ile Phe Val Asp Leu Leu Ala  
 455 460

<210> 12  
 <211> 758  
 <212> PRT



&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 1733477CD1

&lt;400&gt; 12

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Met Gly Leu Ala Asp Ala Ser Gly Pro Arg Asp Thr Gln Ala Leu
 1          5          10          15
Leu Ser Ala Thr Gln Ala Met Asp Leu Arg Arg Arg Asp Tyr His
 20          25          30
Met Glu Arg Pro Leu Leu Asn Gln Glu His Leu Glu Glu Leu Gly
 35          40          45
Arg Trp Gly Ser Ala Pro Arg Thr His Gln Trp Arg Thr Trp Leu
 50          55          60
Gln Cys Ser Arg Ala Arg Ala Tyr Ala Leu Leu Leu Gln His Leu
 65          70          75
Pro Val Leu Val Trp Leu Pro Arg Tyr Pro Val Arg Asp Trp Leu
 80          85          90
Leu Gly Asp Leu Leu Ser Gly Leu Ser Val Ala Ile Met Gln Leu
 95          100         105
Pro Gln Gly Leu Ala Tyr Ala Leu Leu Ala Gly Leu Pro Pro Val
 110         115         120
Phe Gly Leu Tyr Ser Ser Phe Tyr Pro Val Phe Ile Tyr Phe Leu
 125         130         135
Phe Gly Thr Ser Arg His Ile Ser Val Gly Thr Phe Ala Val Met
 140         145         150
Ser Val Met Val Gly Gly Val Thr Glu Ser Leu Ala Pro Gln Ala
 155         160         165
Leu Asn Asp Ser Met Ile Asn Glu Thr Ala Arg Asp Ala Ala Arg
 170         175         180
Val Gln Val Ala Ser Thr Leu Ser Val Leu Val Gly Leu Phe Gln
 185         190         195
Val Gly Leu Gly Leu Ile His Phe Gly Phe Val Val Thr Tyr Leu
 200         205         210
Ser Glu Pro Leu Val Arg Gly Tyr Thr Thr Ala Ala Ala Val Gln
 215         220         225
Val Phe Val Ser Gln Leu Lys Tyr Val Phe Gly Leu His Leu Ser
 230         235         240
Ser His Ser Gly Pro Leu Ser Leu Ile Tyr Thr Val Leu Glu Val
 245         250         255
Cys Trp Lys Leu Pro Gln Ser Lys Val Gly Thr Val Val Thr Ala
 260         265         270
Ala Val Ala Gly Val Val Leu Val Val Val Lys Leu Leu Asn Asp
 275         280         285
Lys Leu Gln Gln Gln Leu Pro Met Pro Ile Pro Gly Glu Leu Leu
 290         295         300
Thr Leu Ile Gly Ala Thr Gly Ile Ser Tyr Gly Met Gly Leu Lys
 305         310         315
His Arg Phe Glu Val Asp Val Val Gly Asn Ile Pro Ala Gly Leu
 320         325         330
Val Pro Pro Val Ala Pro Asn Thr Gln Leu Phe Ser Lys Leu Val
 335         340         345
Gly Ser Ala Phe Thr Ile Ala Val Val Gly Phe Ala Ile Ala Ile
 350         355         360

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Ser Leu Gly Lys Ile Phe Ala Leu Arg His Gly Tyr Arg Val Asp		
	365	370 375
Ser Asn Gln Glu Leu Val Ala Leu Gly Leu Ser Asn Leu Ile Gly		
	380	385 390
Gly Ile Phe Gln Cys Phe Pro Val Ser Cys Ser Met Ser Arg Ser		
	395	400 405
Leu Val Gln Glu Ser Thr Gly Gly Asn Ser Gln Val Ala Gly Ala		
	410	415 420
Ile Ser Ser Leu Phe Ile Leu Leu Ile Ile Val Lys Leu Gly Glu		
	425	430 435
Leu Phe His Asp Leu Pro Lys Ala Val Leu Ala Ala Ile Ile Ile		
	440	445 450
Val Asn Leu Lys Gly Met Leu Arg Gln Leu Ser Asp Met Arg Ser		
	455	460 465
Leu Trp Lys Ala Asn Arg Ala Asp Leu Leu Ile Trp Leu Val Thr		
	470	475 480
Phe Thr Ala Thr Ile Leu Leu Asn Leu Asp Leu Gly Leu Val Val		
	485	490 495
Ala Val Ile Phe Ser Ser Leu Leu Val Val Val Arg Thr Gln Met		
	500	505 510
Pro His Tyr Ser Val Leu Gly Gln Val Pro Asp Thr Asp Ile Tyr		
	515	520 525
Arg Asp Val Ala Glu Tyr Ser Glu Ala Lys Glu Val Arg Gly Val		
	530	535 540
Lys Val Phe Arg Ser Ser Ala Thr Val Tyr Phe Ala Asn Ala Glu		
	545	550 555
Phe Tyr Ser Asp Ala Leu Lys Gln Arg Cys Gly Val Asp Val Asp		
	560	565 570
Phe Leu Ile Ser Gln Lys Lys Lys Leu Leu Lys Lys Gln Glu Gln		
	575	580 585
Leu Lys Leu Lys Gln Leu Gln Lys Glu Glu Lys Leu Arg Lys Gln		
	590	595 600
Ala Ala Ser Pro Lys Gly Ala Ser Val Ser Ile Asn Val Asn Thr		
	605	610 615
Ser Leu Glu Asp Met Arg Ser Asn Asn Val Glu Asp Cys Lys Met		
	620	625 630
Met Val Ser Ser Gly Asp Lys Met Glu Asp Ala Thr Ala Asn Gly		
	635	640 645
Gln Glu Asp Ser Lys Ala Pro Asp Gly Ser Thr Leu Lys Ala Leu		
	650	655 660
Gly Leu Pro Gln Pro Asp Phe His Ser Leu Ile Leu Asp Leu Gly		
	665	670 675
Ala Leu Ser Phe Val Asp Thr Val Cys Leu Lys Ser Leu Lys Asn		
	680	685 690
Ile Phe His Asp Phe Arg Glu Ile Glu Val Glu Val Tyr Met Ala		
	695	700 705
Ala Cys His Ser Pro Val Val Ser Gln Leu Glu Ala Gly His Phe		
	710	715 720
Phe Asp Ala Ser Ile Thr Lys Lys His Leu Phe Ala Ser Val His		
	725	730 735
Asp Ala Val Thr Phe Ala Leu Gln His Pro Arg Pro Val Pro Asp		
	740	745 750
Ser Pro Val Ser Val Thr Arg Leu		
	755	

<210> 13  
 <211> 336  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <223> Incyte ID No: 2641908CD1

<400> 13  
 Met Met Gly Pro Gly Leu Ala Phe Gly Leu Gly Ser Leu Met Leu  
 1 5 10 15  
 Arg Leu Tyr Val Asp Ile Asn Gln Met Pro Glu Gly Gly Ile Ser  
 20 25 30  
 Leu Thr Ile Lys Asp Pro Arg Trp Val Gly Ala Trp Trp Leu Gly  
 35 40 45  
 Phe Leu Ile Ala Ala Gly Ala Val Ala Leu Ala Ala Ile Pro Tyr  
 50 55 60  
 Phe Phe Phe Pro Lys Glu Met Pro Lys Glu Lys Arg Glu Leu Gln  
 65 70 75  
 Phe Arg Arg Lys Val Leu Ala Val Thr Asp Ser Pro Ala Arg Lys  
 80 85 90  
 Gly Lys Asp Ser Pro Ser Lys Gln Ser Pro Gly Glu Ser Thr Lys  
 95 100 105  
 Lys Gln Asp Gly Leu Val Gln Ile Ala Pro Asn Leu Thr Val Ile  
 110 115 120  
 Gln Phe Ile Lys Val Phe Pro Arg Val Leu Leu Gln Thr Leu Arg  
 125 130 135  
 His Pro Ile Phe Leu Leu Val Val Leu Ser Gln Val Cys Leu Ser  
 140 145 150  
 Ser Met Ala Ala Gly Met Ala Thr Phe Leu Pro Lys Phe Leu Glu  
 155 160 165  
 Arg Gln Phe Ser Ile Thr Ala Ser Tyr Ala Asn Leu Leu Ile Gly  
 170 175 180  
 Cys Leu Ser Phe Pro Ser Val Ile Val Gly Ile Val Val Gly Gly  
 185 190 195  
 Val Leu Val Lys Arg Leu His Leu Gly Pro Val Gly Cys Gly Ala  
 200 205 210  
 Leu Cys Leu Leu Gly Met Leu Leu Cys Leu Phe Phe Ser Leu Pro  
 215 220 225  
 Leu Phe Phe Ile Gly Cys Ser Ser His Gln Ile Ala Gly Ile Thr  
 230 235 240  
 His Gln Thr Ser Ala His Pro Gly Leu Glu Leu Ser Pro Ser Cys  
 245 250 255  
 Met Glu Ala Cys Ser Cys Pro Leu Asp Gly Phe Asn Pro Val Cys  
 260 265 270  
 Asp Pro Ser Thr Arg Val Glu Tyr Ile Thr Pro Cys His Ala Gly  
 275 280 285  
 Cys Ser Ser Trp Val Val Gln Asp Ala Leu Asp Asn Ser Gln Ser  
 290 295 300  
 Pro Pro Thr Ser His Pro His Ala Gly His Gln His Leu Asn Leu  
 305 310 315  
 Arg Leu Leu Gln Gly Glu Thr Trp Ala Ala Leu Ala Gly Ala Glu  
 320 325 330  
 Glu Pro Val Asp Gly Ala

335

<210> 14  
 <211> 103  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <223> Incyte ID No: 2656554CD1

<400> 14  
 Met Glu Arg Gln Ser Arg Val Met Ser Glu Lys Asp Glu Tyr Gln  
 1 5 10 15  
 Phe Gln His Gln Gly Ala Val Glu Leu Leu Val Phe Asn Phe Leu  
 20 25 30  
 Leu Ile Leu Thr Ile Leu Thr Ile Trp Leu Phe Lys Asn His Arg  
 35 40 45  
 Phe Arg Phe Leu His Glu Thr Gly Gly Ala Met Val Tyr Asp Lys  
 50 55 60  
 Pro Pro Lys Phe Ala Met Ser Arg Glu Gln Met Ser Gln Ser Cys  
 65 70 75  
 Ser His Thr Ala His Asn Ala Ser Leu Leu Thr Asp Ala Gly Pro  
 80 85 90  
 Leu Ser Cys Gly Glu Ser Arg Ala Ser Cys Leu Phe Leu  
 95 100

<210> 15  
 <211> 123  
 <212> PRT  
 <213> Homo sapiens

<220>  
 <221> misc\_feature  
 <223> Incyte ID No: 2719228CD1

<400> 15  
 Met Gln Gly Met Gly Leu Gly Leu Ser Ser Val Phe Ala Leu Cys  
 1 5 10 15  
 Leu Gly His Thr Ser Ser Phe Cys Glu Ser Val Val Phe Ala Ser  
 20 25 30  
 Ala Ser Ile Gly Leu Gln Thr Phe Asn His Ser Gly Ile Ser Val  
 35 40 45  
 Asn Ile Gln Asp Leu Ala Pro Ser Cys Ala Gly Phe Leu Phe Gly  
 50 55 60  
 Val Ala Asn Thr Ala Gly Ala Leu Ala Gly Val Val Gly Val Cys  
 65 70 75  
 Leu Gly Gly Tyr Leu Met Glu Thr Thr Gly Ser Trp Thr Cys Leu  
 80 85 90  
 Phe Asn Leu Val Ala Ile Ile Ser Asn Leu Gly Leu Cys Thr Phe  
 95 100 105  
 Leu Val Phe Gly Gln Ala Gln Arg Val Asp Leu Ser Ser Thr His  
 110 115 120

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PCT/US99/26048

Glu Asp Leu

<210> 16  
<211> 222  
<212> PRT  
<213> Homo sapiens

<220>  
<221> misc\_feature  
<223> Incyte ID No: 3657824CD1

<400> 16  
Met Lys Gln Glu Ser Ala Ala Pro Asn Thr Pro Pro Thr Ser Gln  
1 5 10 15  
Ser Pro Thr Pro Ser Ala Gln Phe Pro Arg Asn Asp Gly Asp Pro  
20 25 30  
Gln Ala Leu Trp Ile Phe Gly Tyr Gly Ser Leu Val Trp Arg Pro  
35 40 45  
Asp Phe Ala Tyr Ser Asp Ser Arg Val Gly Phe Val Arg Gly Tyr  
50 55 60  
Ser Arg Arg Phe Trp Gln Gly Asp Thr Phe His Arg Gly Ser Asp  
65 70 75  
Lys Met Pro Gly Arg Val Val Thr Leu Leu Glu Asp His Glu Gly  
80 85 90  
Cys Thr Trp Gly Val Ala Tyr Gln Val Gln Gly Glu Gln Val Ser  
95 100 105  
Lys Ala Leu Lys Tyr Leu Asn Val Arg Glu Ala Val Leu Gly Gly  
110 115 120  
Tyr Asp Thr Lys Glu Val Thr Phe Tyr Pro Gln Asp Ala Pro Asp  
125 130 135  
Gln Pro Leu Lys Ala Leu Ala Tyr Val Ala Thr Pro Gln Asn Pro  
140 145 150  
Gly Tyr Leu Gly Pro Ala Pro Glu Glu Ala Ile Ala Thr Gln Ile  
155 160 165  
Leu Ala Cys Arg Gly Phe Ser Gly His Asn Leu Glu Tyr Leu Leu  
170 175 180  
Arg Leu Ala Asp Phe Met Gln Leu Cys Gly Pro Gln Ala Gln Asp  
185 190 195  
Glu His Leu Ala Ala Ile Val Asp Ala Val Gly Thr Met Leu Pro  
200 205 210  
Cys Phe Cys Pro Thr Glu Gln Ala Leu Ala Leu Val  
215 220

<210> 17  
<211> 111  
<212> PRT  
<213> Homo sapiens

<220>  
<221> misc\_feature  
<223> Incyte ID No: 5378485CD1

<400> 17  
Met Leu Ser Ala Leu Pro Gly Trp Gly Pro Ala His Leu Gln Arg

1	5	10	15
Pro Leu Leu Gly	Pro Ala Ser Cys Leu Gly Ile Leu Arg Pro Ala		
	20	25	30
Met Thr Ala His Ser Phe Ala Leu Pro Val Ile Ile Phe Thr Thr			
	35	40	45
Phe Trp Gly Leu Val Gly Ile Ala Gly Pro Trp Phe Val Pro Lys			
	50	55	60
Gly Pro Asn Arg Gly Val Ile Ile Thr Met Leu Val Ala Thr Ala			
	65	70	75
Val Cys Cys Tyr Leu Phe Trp Leu Ile Ala Ile Leu Ala Gln Leu			
	80	85	90
Asn Pro Leu Phe Gly Pro Gln Leu Lys Asn Glu Thr Ile Trp Tyr			
	95	100	105
Val Arg Phe Leu Trp Glu			
	110		

&lt;210&gt; 18

&lt;211&gt; 1303

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 961344CB1

&lt;400&gt; 18

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ccccacgcgc cgccccacgcg tccgcaagat atggatgcta acaggcgata aactcgagac 60
agctacctgc attgccaaaa gttcacatct cgtgtctaga acacaagata ttcataat 120
cagacaggta accagtcggg gagaggcaca tttggagctg aatgcatttc gaaggaagca 180
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&lt;211&gt; 1475

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 2466714CB1

&lt;400&gt; 24

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&lt;210&gt; 25

&lt;211&gt; 1793

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 2617942CB1

&lt;400&gt; 25

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&lt;210&gt; 26

&lt;211&gt; 1141

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 2945431CB1

&lt;400&gt; 26

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&lt;210&gt; 27

&lt;211&gt; 1371

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 4074113CB1

&lt;400&gt; 27

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&lt;211&gt; 2752

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 1413743CB1

&lt;400&gt; 28

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&lt;211&gt; 2580

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&lt;213&gt; Homo sapiens

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&lt;223&gt; Incyte ID No: 1733477CB1

&lt;400&gt; 29

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&lt;213&gt; Homo sapiens

&lt;220&gt;

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&lt;223&gt; Incyte ID No: 2641908CB1

&lt;400&gt; 30

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gggtgatatt taagctgaaa ggaatagaaa tgatgatgac agcaactcgc ccctctacct 180
cgggatacctg tttgcagtga ccatgatggg gccaggcctg gcctttgggc tgggcagcct 240
catgctgcgc ctttatgtgg acattaacca gatgccagaa ggtggtatca gcctgacct 300
aaaggacccc cgatgggtgg gtgcctgggt gctgggtttc ctcatcgtc ccggtgcagt 360
ggccctggct gccatccctt acttcttctt cccaaggaa atgcccaagg aaaaacgtga 420
gcttcagttt cggcgaaagg tcttagcagt cacagactca cctgccagga agggcaagga 480

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WO 00/26245

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ctctccctct aagcagagcc ctggggagtc cacgaagaag caggatggcc tagtccagat 540
tgacacaaac ctgactgtga tccagttcat taaagtcttc cccaggggtgc tgctgcagac 600
cctacgccac cccatcttcc tgetgggtgt cctgtccag gtatgcttgt catccatggc 660
tgccggcatg gccaccttcc tgcccaagtt cctggagcgc cagttttcca tcacagctc 720
ctacgccaac ctgctcatcg gctgectctc cttcccttcg gtcacgtgg gcatcgtgg 780
gggtggcgtc ctggtcaagc ggctccacct ggccctgtg ggatgcgggtg ccctttgcct 840
gctggggatg ctgctgtgcc tcttcttcag cctgcgctc ttctttatcg gctgctccag 900
ccaccagatt gcgggcatca cacaccagac cagtgcacac cctgggctgg agctgtctcc 960
aagctgcatg gaggcctgct cctgcccatt ggaaggcttt aaccctgtct gcgacccag 1020
cactcgtgtg gaatacatca caccctgcca cgcaggctgc tcaagctggg tgggtccagga 1080
tgctctggac aacagccaga gtctccccc ctcccacct catgctgggc atcagcatct 1140
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gagaccccca ggccttggca ggtggagcag tgaactcctg tggatatggg aaccgattca 1320
aatccttctt aggcctctaa ctgactctgt taccttaggc aaattattta actagtgcct 1380
cagtttcttg gtctgtaaaa taggggagat attattaagt gcctactaca gagcaggaat 1440
gtgctgaata aatgctttac ctggatgaaa aaaaaaaaaa a 1481

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&lt;210&gt; 31

&lt;211&gt; 667

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 2656554CB1

&lt;400&gt; 31

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ctaaagtggc agtgtttctt ctgaaattct caggcagtca gactgtctta ggcaaattct 60
gataaaaatag cccttatcca ggtttttatc taaggaaatcc caagaagact ggggaatgga 120
gagacagtca agggttatgt cagaaaagga tgagtatcag tttcaacatc agggagcggg 180
ggagctgctt gtcttcaatt tttgtctcat ccttaccatt ttgacaatct ggttatttta 240
aaatcatcga ttccgcttct tgcatgaaac tggaggagca atggtgtatg acaagccgcc 300
gaaatttgcc atgtcacgag agcaaatgtc acagtcatgt tctcacacgg cacataatgc 360
aagtctgttg acagatgcgg gtccattgtc atgtggggag tgcagggcga gctgtttgtt 420
tttgtaatga tgttgggaag tgatggctct gcagtcacaa agagcagcct tctctcactg 480
gctgcaccga tgaacattac gaagttctag aaaaaacatc acttcaaaat gcctggagta 540
attcctctta tatcaactaa tttcaagaag aaaacttgca gaaactaacc ccacctctct 600
taagagaata ttgtgtccaa gtccttttta tttatacgaa cagtgtctta ttttcttata 660
atgaaat

```

&lt;210&gt; 32

&lt;211&gt; 1635

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 2719228CB1

&lt;400&gt; 32

```

atagctgtct tgagccccaa gcctcttctt cccctgctgc ccctctgcag ccattcggga 60
tgggaccccc tctgggggtgt cagcacgaaa gggctaacgg gagccccctt cttggcctcc 120

```

```

ccctgtaggt tacagagcca tcacggtgcg gaagctcatg cagggcatgg gccttggcct 180
ctccagcgtc tttgctctgt gcctgggcca cacctccagc ttctgtgagt ctgtggtctt 240
tgcacagacc tccatcggcc tccagacctt caaccacagt ggcatttctg ttaacatcca 300
ggacttggcc cegtcctgcg cgggctttct gtttggtgtg gccaacacag cgggggcctt 360
ggcagggtgc gtgggtgtgt gtctaggcgg ctacttgatg gagaccacgg gctcctggac 420
ttgcctgttc aaccttgtgg ccatcatcag caacctgggg ctgtgcacct tcctggtgtt 480
tggacaggct cagagggtgg acctgagctc taccatgag gacctctagc tccaacccc 540
acagcctctc caaggaccca ggcgccagca gcccggggac acaggggact cagtgtgtga 600
gacttgggtc ctccatgtca gacacacgag cagagaggaa cacaacccac tgtggagcct 660
gaagctcctt aagaagagtc cacaacagct ggtgggaggg tggggtgggc ctgggtccag 720
accaggctcg ctgctctctg ggctcagtt tccccacctg ccagcgggct cggccctgtc 780
ctcctcacag gctggtgtgg cgtcagggtt ggggtggggtt attgttagta ggcgcagcct 840
cattcccacc acgatctgtt cgcgtgggtt cccgccaaac ctccctcggc cgcctgttc 900
tccgaagcc tctgcagcg cccgcctgcc aatgtgaggc tggcaccagg ctgcagcctc 960
cccaatccca gccactttg ctgtgtctct ggcgggctgt cctccttggc gggagctgtc 1020
ctgcacactg taggatgtct aaaggtatcc ctggcctcca cccaccctta gccagcagct 1080
cccagtcaga caacagccag aaatgtctcc agactctgcc cagcctcccc aggtagccac 1140
cctcgagaca cgacctcaga gtctctgtgt ctctagaag cctgacagag accccaggc 1200
cagtgggtgg gtggcgggct agagaccctt gcctgtgtcc gggaccctgg cgcctctc 1260
ccctcctgtg gatccctccg cactaacagt gttctcagt ggcagacgcc tgggcacccc 1320
ttgggcccctg cccagcatgg ccatggcgca ggctctcgaa cccgcatggc tttcccaggc 1380
ctggtgattc tgcctccag ggacggttgg cacccttctc gggggcgggc cccacgcacc 1440
ccagaacaca cagaccacc tttctggcgt tctttctacc tccctttctg ttgctgagg 1500
agctggtggt tcatgagtt aatgatacat cttgcaaggt gtacacatag agaaaaaac 1560
ctaaaaatgt ggaagacac gccaaagcct tatttaaata ataactatta aactattcaa 1620
aaagaaaaaa aaaaaa                                     1635

```

&lt;210&gt; 33

&lt;211&gt; 1447

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc\_feature

&lt;223&gt; Incyte ID No: 3657824CB1

&lt;400&gt; 33

```

ccgagcgggtg ccaggccagg tgtgtgcgtc cgtcggctct tccgtgccc cgcgggagac 60
cagccccgga ggcgcctgg gcctatccct gtgccaggca ccatgaagca ggagtctgca 120
gccccgaaca ccccgccac ctgcagctcc cctacgcct cgcctcagtt cccccgaaac 180
gacggcgacc ctcaagcgt gtggatttct gggtagcgt ccttgggtgt gaggcccgac 240
ttcgctaca gcgacagcg tgtgggcttc gtgcgggct acagcgcgg tttctggcag 300
ggagacacct tccatcgggg cagcgacaag atgcctggcc gtgtggtgac gctccttgaa 360
gatcatgagg gctgcacttg gggcgtggca taccaagtgc aaggggagca ggtaagcaag 420
gccctgaagt acctgaatgt gcgagaggca gtgcttgggt gctacgatac caaggaggtc 480
accttctatc cccaagatgc tctgaccaa cactgaagg cattggccta tgtggccacc 540
ccacagaacc ctggttacct gggccctgcg cctgaagagg ccattgccac gcagatcctg 600
gcctgcggg gcttctccgg ccacaacctt gaatacttgc tgcgtctggc agacttcatg 660
cagctctgtg ggcctcaggc gcaggacgag cactggcag ccatcgtgga cgtgtgggc 720
accatgttgc cctgcttctg cccaccagag caggctctgg cgtggtgtg aggggctgag 780
ccccgcggg gagtgtcat gtggacatca gggccagaca cccactccag tgcacaagac 840
agacttgca cgccttgagc cactgagca gatatggtg gtggctggag gcttctctt 900
ctcagtcctt gcctgtctgc cagcctgcag ctctcctgct tgacactgac ttactactg 960
aaactttatt tattgcacca tgttgggtgt gtgggcaggg ggagggcctg ccctggacac 1020

```

agggggccctg ctgagcagtg gccccatcct ggaacttgac cagattcccc ccagtgtgtc 1080  
 tgctaacccc acaccaccca ggcctccacc tccccaggga gtctccaaga gcctcgatcc 1140  
 tctgtctact cagcccagcc atccatagcc ctgggaattc cacctgcca ggatcccagc 1200  
 aggtctggatg agggatagta gggcatgagg agaaggagcc ctgtaaggac tgaggccccg 1260  
 gccagccctt ctctccacc agttccccag agcagagctg gagctgatgc ctggacacag 1320  
 ctgctgagcc tggcctgggc ctcttaccga cttggtgtt ttctgtccc tctgtctgtc 1380  
 tgtctatcta cttgtctgtc tgggcccactc ctgctgtgt gttggtctat tcttgggaag 1440  
 ctcacata 1447

&lt;210&gt; 34

&lt;211&gt; 657

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;220&gt;

&lt;221&gt; misc feature

&lt;223&gt; Incyte ID No: 5378485CB1

&lt;400&gt; 34

gactcctgtt gcgcagctc agcgcgctgc ccggtgggg acccgcgac ctgcagcgcc 60  
 cgctgctgg cctgcaccc tgcctgggca tctgcgccc ggccatgac gcgcactcat 120  
 tcgcccctcc ggtcatcatc ttcaccacgt tctggggcct cgtcggcatc gccggggccct 180  
 ggttcgtgcc gaagggaccc aaccgaggag tgatcatcac catgctggtc gccaccggcc 240  
 tctgtgttta cctcttctgg ctcatcgcca tctggcgca gctgaacccc ctgttcgggc 300  
 cccagctgaa gaatgagacc atctggtacg tgcgcttct gtgggagtga cccggcgccc 360  
 ccgaccagg tgcccagctc tgggaatgac tgtggtcca ctgtccctga caacccttc 420  
 gtccggaccc tccccacac aactatgtct ggtcaccagc tccctcctgc tggcaccag 480  
 agaccgggac ccgaggcccc tgcctgggtc ctggaagtct tcccagctt cccagccagc 540  
 ccggggccct ggggagccct gggcacagca gcggccgagg ggatgtcctg ctccaatact 600  
 cgcactgctc tggagtttgc actctttcgc aaggagatgc tgctggggag ctggtat 657

&lt;210&gt; 35

&lt;211&gt; 646

&lt;212&gt; PRT

&lt;213&gt; Mus musculus

&lt;300&gt;

&lt;308&gt; GenBank ID No: g2612939

&lt;400&gt; 35

Met	Arg	Ala	Pro	Gly	Ala	Gly	Thr	Ala	Ser	Val	Ala	Ser	Leu	Ala
1				5					10					15
Leu	Leu	Trp	Phe	Leu	Gly	Leu	Pro	Trp	Thr	Trp	Ser	Ala	Ala	Ala
				20					25					30
Ala	Phe	Cys	Val	Tyr	Val	Gly	Gly	Gly	Gly	Trp	Arg	Phe	Leu	Arg
				35					40					45
Ile	Val	Cys	Lys	Thr	Ala	Arg	Arg	Asp	Leu	Phe	Gly	Leu	Ser	Val
				50					55					60
Leu	Ile	Arg	Val	Arg	Leu	Glu	Leu	Arg	Arg	His	Arg	Arg	Ala	Gly
				65					70					75
Asp	Thr	Ile	Pro	Cys	Ile	Phe	Gln	Ala	Val	Ala	Arg	Arg	Gln	Pro
				80					85					90
Glu	Arg	Leu	Ala	Val	Asp	Ala	Ser	Ser	Gly	Ile	Cys	Trp	Thr	
				95					100					105

Phe	Ala	Gln	Leu	Asp	Thr	Tyr	Ser	Asn	Ala	Val	Ala	Asn	Leu	Phe
				110					115					120
Arg	Gln	Leu	Gly	Phe	Ala	Pro	Gly	Asp	Val	Val	Ala	Val	Phe	Leu
				125					130					135
Glu	Gly	Arg	Pro	Glu	Phe	Val	Gly	Leu	Trp	Leu	Gly	Leu	Ala	Lys
				140					145					150
Ala	Gly	Val	Val	Ala	Ala	Leu	Leu	Asn	Val	Asn	Leu	Arg	Arg	Glu
				155					160					165
Pro	Leu	Ala	Phe	Cys	Leu	Gly	Thr	Ser	Ala	Ala	Lys	Ala	Leu	Ile
				170					175					180
Tyr	Gly	Gly	Glu	Met	Ala	Ala	Ala	Val	Ala	Glu	Val	Ser	Glu	Gln
				185					190					195
Leu	Gly	Lys	Ser	Leu	Leu	Lys	Phe	Cys	Ser	Gly	Asp	Leu	Gly	Pro
				200					205					210
Glu	Ser	Ile	Leu	Pro	Asp	Thr	Gln	Leu	Leu	Asp	Pro	Met	Leu	Ala
				215					220					225
Glu	Ala	Pro	Thr	Thr	Pro	Leu	Ala	Gln	Ala	Pro	Gly	Lys	Gly	Met
				230					235					240
Asp	Asp	Arg	Leu	Phe	Tyr	Ile	Tyr	Thr	Ser	Gly	Thr	Thr	Gly	Leu
				245					250					255
Pro	Lys	Ala	Ala	Ile	Val	Val	His	Ser	Arg	Tyr	Tyr	Arg	Ile	Ala
				260					265					270
Ala	Phe	Gly	His	His	Ser	Tyr	Ser	Met	Arg	Ala	Ala	Asp	Val	Leu
				275					280					285
Tyr	Asp	Cys	Leu	Pro	Leu	Tyr	His	Ser	Ala	Gly	Asn	Ile	Met	Gly
				290					295					300
Val	Gly	Gln	Cys	Val	Ile	Tyr	Gly	Leu	Thr	Val	Val	Leu	Arg	Lys
				305					310					315
Lys	Phe	Ser	Ala	Ser	Arg	Phe	Trp	Asp	Asp	Cys	Val	Lys	Tyr	Asn
				320					325					330
Cys	Thr	Val	Val	Gln	Tyr	Ile	Gly	Glu	Ile	Cys	Arg	Tyr	Leu	Leu
				335					340					345
Arg	Gln	Pro	Val	Arg	Asp	Val	Glu	Gln	Arg	His	Arg	Val	Arg	Leu
				350					355					360
Ala	Val	Gly	Asn	Gly	Leu	Arg	Pro	Ala	Ile	Trp	Glu	Glu	Phe	Thr
				365					370					375
Gln	Arg	Phe	Gly	Val	Pro	Gln	Ile	Gly	Glu	Phe	Tyr	Gly	Ala	Thr
				380					385					390
Glu	Cys	Asn	Cys	Ser	Ile	Ala	Asn	Met	Asp	Gly	Lys	Val	Gly	Ser
				395					400					405
Cys	Gly	Phe	Asn	Ser	Arg	Ile	Leu	Thr	His	Val	Tyr	Pro	Ile	Arg
				410					415					420
Leu	Val	Lys	Val	Asn	Glu	Asp	Thr	Met	Glu	Pro	Leu	Arg	Asp	Ser
				425					430					435
Glu	Gly	Leu	Cys	Ile	Pro	Cys	Gln	Pro	Gly	Glu	Pro	Gly	Leu	Leu
				440					445					450
Val	Gly	Gln	Ile	Asn	Gln	Gln	Asp	Pro	Leu	Arg	Arg	Phe	Asp	Gly
				455					460					465
Tyr	Val	Ser	Asp	Ser	Ala	Thr	Asn	Lys	Lys	Ile	Ala	His	Ser	Val
				470					475					480
Phe	Arg	Lys	Gly	Asp	Ser	Ala	Tyr	Leu	Ser	Gly	Asp	Val	Leu	Val
				485					490					495
Met	Asp	Glu	Leu	Gly	Tyr	Met	Tyr	Phe	Arg	Asp	Arg	Ser	Gly	Asp
				500					505					510
Thr	Phe	Arg	Trp	Arg	Gly	Glu	Asn	Val	Ser	Thr	Thr	Glu	Val	Glu

	515	520	525
Ala Val Leu Ser Arg Leu Leu Gly Gln Thr Asp Val Ala Val Tyr			
	530	535	540
Gly Val Ala Val Pro Gly Val Glu Gly Lys Ala Gly Met Ala Ala			
	545	550	555
Ile Ala Asp Pro His Ser Gln Leu Asp Pro Asn Ser Met Tyr Gln			
	560	565	570
Glu Leu Gln Lys Val Leu Ala Ser Tyr Ala Arg Pro Ile Phe Leu			
	575	580	585
Arg Leu Leu Pro Gln Val Asp Thr Thr Gly Thr Phe Lys Ile Gln			
	590	595	600
Lys Thr Arg Leu Gln Arg Glu Gly Phe Asp Pro Arg Gln Thr Ser			
	605	610	615
Asp Arg Leu Phe Phe Leu Asp Leu Lys Gln Gly Arg Tyr Val Pro			
	620	625	630
Leu Asp Glu Arg Val His Ala Arg Ile Cys Ala Gly Asp Phe Ser			
	635	640	645
Leu			

&lt;210&gt; 36

&lt;211&gt; 691

&lt;212&gt; PRT

&lt;213&gt; Schistosoma mansoni

&lt;300&gt;

&lt;308&gt; GenBank ID No: g425474

&lt;400&gt; 36

Met Phe Ser Ala Leu Cys Arg Arg Gly Phe Leu Thr Asn Lys Val		
1	5	10
Ser Gln Phe Arg Ser Thr Tyr Lys Cys Asp His Tyr Asn Leu Lys		15
	20	25
Thr His Ile Lys Pro Leu Lys Cys Ser Ser Ser Leu Arg Leu Thr		30
	35	40
Val Gly Thr Gly Leu Phe Ile Ala Leu His Ser Lys Ile Ser Pro		45
	50	55
Glu Ser Arg Ile Gln Thr Val Gln Cys Glu Val Asp Ser Tyr Gln		60
	65	70
Thr Asp Gln Ile Thr Phe Ala Lys Ser Gly Gly Ile Pro Arg Tyr		75
	80	85
Ile Gly Val Leu Ile Leu Pro Asp Cys Val Tyr Leu Phe Gly Ala		90
	95	100
Ile Leu Gly Ala Phe Val Ala Ala Val Met Asn Val Tyr Ile Pro		105
	110	115
Leu Tyr Leu Gly Asp Phe Val Ser Ser Leu Ser Arg Cys Val Val		120
	125	130
Thr His Glu Gly Phe Val Ser Ala Val Tyr Val Pro Thr Leu Arg		135
	140	145
Leu Cys Ser Ser Tyr Leu Leu Gln Ser Leu Ser Thr Phe Leu Tyr		150
	155	160
Ile Gly Leu Leu Gly Ser Val Gly Glu Arg Met Ala Arg Arg Met		165
	170	175
Arg Ile Gln Leu Phe Arg Lys Leu Val Tyr Gln Asp Val Ala Tyr		180
	185	190
		195

Phe Asp Val His Ser Ser Gly Lys Leu Val Glu Ile Ile Gly Ser	200	205	210
Asp Val Gln Asn Phe Lys Ser Ser Phe Lys Gln Cys Ile Ser Gln	215	220	225
Gly Leu Arg Asn Gly Ile Gln Val Val Gly Ser Val Phe Ala Leu	230	235	240
Leu Ser Ile Ser Pro Thr Leu Thr Ala Ala Leu Ile Gly Cys Leu	245	250	255
Pro Cys Val Phe Leu Ile Gly Ser Leu Met Gly Thr Glu Leu Arg	260	265	270
His Ile Ser Arg Glu Val Gln Ser Gln Asn Ser Leu Phe Ala Ser	275	280	285
Leu Ile Asp Glu Ala Phe Ser His Ile Arg Thr Val Lys Ser Leu	290	295	300
Ala Met Glu Asp Phe Leu Ile Asn Lys Ile Asn Tyr Asn Val Asp	305	310	315
Lys Ala Lys Met Leu Ser Glu Lys Leu Ser Phe Gly Ile Gly Ser	320	325	330
Phe Gln Gly Leu Ser Asn Leu Thr Leu Asn Gly Val Val Leu Gly	335	340	345
Val Leu Tyr Val Gly Gly His Leu Met Ser Arg Gly Glu Leu Asp	350	355	360
Ala Gly His Leu Met Ser Phe Leu Ala Thr Thr Gln Thr Leu Gln	365	370	375
Arg Ser Leu Thr Gln Leu Ser Leu Leu Tyr Gly Gln Val Val Arg	380	385	390
Gly Tyr Thr Ala Leu Lys Arg Ile His Asp Ile Leu Ala Leu Pro	395	400	405
Ser Gly Ile Gly Ser Ile Pro Ser Ser Ser Ser Ser Leu Val Val	410	415	420
Ser Lys Gln His Val Asn Asn Ile Lys Glu Leu Pro Ser Ser Ser	425	430	435
Ile Tyr Ser Ala Pro Ser Ile Glu Phe Ser Asp Val Lys Phe Ala	440	445	450
Tyr Pro Asn Arg Pro Glu Thr Ile Val Leu Asn Glu Leu Ser Met	455	460	465
Phe Leu Pro Gly Gly Lys Val Ile Ala Leu Val Gly Gln Ser Gly	470	475	480
Ala Gly Lys Ser Thr Val Val Ser Leu Leu Glu Arg Phe Tyr Asp	485	490	495
Pro Ile Ser Gly Glu Ile Leu Leu Asn Gly Asp Lys Leu Thr Asn	500	505	510
Phe Asn Val Asn Tyr Leu Arg Ser Lys Leu Ile Gly Tyr Ile Ser	515	520	525
Gln Glu Pro Gln Ile Phe Asn Ala Ser Ile Arg Glu Asn Ile Arg	530	535	540
Phe Gly Arg Phe Asp Ala Thr Asp Glu Glu Val Glu Glu Ala Ala	545	550	555
Lys Leu Ala Tyr Ala His Asp Phe Ile Ser Asn Asp Leu Pro Tyr	560	565	570
Gly Tyr Asp Thr Leu Val Gly Gln Gly Thr Gly Thr Ile Ala Gly	575	580	585
Leu Ser Gly Gly Gln Arg Gln Arg Ile Ala Ile Ala Arg Ile Leu	590	595	600
Leu Lys Asn Ala Pro Ile Leu Leu Met Asp Glu Ala Thr Ser Ala			

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605	610	615
Leu Asp Thr Glu Ser Glu Ala Lys Val	Gln Asn Ala Leu Asn Asn	
620	625	630
Ala Met Lys Gly Arg Thr Val Leu Ile	Ile Ala His Arg Leu Ser	
635	640	645
Thr Val Arg Lys Ala Asp Leu Ile Leu	Val Met Ser Lys Gly Gln	
650	655	660
Ile Val Glu Lys Gly Thr His Ser Glu	Leu Met Ala Asn His Gly	
665	670	675
Tyr Tyr Tyr Asn Leu Val Gln Arg Gln	Glu Gly Cys Asp Val Phe	
680	685	690

Asp

&lt;210&gt; 37

&lt;211&gt; 634

&lt;212&gt; PRT

&lt;213&gt; Rattus norvegicus

&lt;300&gt;

&lt;308&gt; GenBank ID No: g3015617

&lt;400&gt; 37

Met Thr Val Ala Ser Thr Ala Ala Pro Ser Tyr Thr Thr Ser Asp	
1	5 10 15
Thr Asn Arg Val Ile Ser Thr Phe Ser Val Val Asp Tyr Val Val	
20	25 30
Phe Gly Leu Leu Leu Val Leu Ser Leu Val Ile Gly Leu Tyr His	
35	40 45
Ala Cys Arg Gly Trp Gly Arg His Thr Val Gly Glu Leu Leu Met	
50	55 60
Ala Asp Arg Lys Met Gly Cys Leu Pro Val Ala Leu Ser Leu Leu	
65	70 75
Ala Thr Phe Gln Ser Ala Val Ala Ile Leu Gly Gly Pro Ala Glu	
80	85 90
Ile Tyr Arg Phe Gly Thr Gln Tyr Trp Phe Leu Gly Cys Ser Tyr	
95	100 105
Phe Leu Gly Leu Leu Ile Pro Ala His Ile Phe Ile Pro Val Phe	
110	115 120
Tyr Arg Leu His Leu Thr Ser Ala Tyr Glu Tyr Leu Glu Leu Arg	
125	130 135
Phe Asn Lys Ala Val Arg Ile Cys Gly Thr Val Thr Phe Ile Phe	
140	145 150
Gln Met Val Val Tyr Met Gly Val Ala Leu Tyr Ala Pro Ser Leu	
155	160 165
Ala Leu Asn Ala Val Thr Gly Phe Asp Leu Trp Leu Ser Val Leu	
170	175 180
Ala Leu Gly Ile Val Cys Asn Ile Tyr Thr Ala Leu Gly Gly Leu	
185	190 195
Lys Ala Val Ile Trp Thr Asp Val Phe Gln Thr Leu Ile Met Phe	
200	205 210
Leu Gly Gln Leu Val Val Ile Ile Val Gly Ala Ala Lys Val Gly	
215	220 225
Gly Leu Gly His Val Trp Ala Val Ala Ser Gln His Gly Leu Ile	
230	235 240

Ser Gly Ile Glu Leu Asp Pro Asp Pro Phe Val Arg His Thr Phe	245	250	255
Trp Thr Leu Ala Phe Gly Gly Val Phe Met Met Leu Ser Leu Tyr	260	265	270
Gly Val Asn Gln Ala Gln Val Gln Arg Tyr Leu Ser Ser His Ser	275	280	285
Glu Lys Ala Ala Val Leu Ser Cys Tyr Ala Val Phe Pro Cys Gln	290	295	300
Gln Val Ala Leu Cys Met Ser Cys Leu Ile Gly Leu Val Met Phe	305	310	315
Ala Tyr Tyr Lys Lys Tyr Ser Met Ser Pro Gln Gln Glu Gln Ala	320	325	330
Ala Pro Asp Gln Leu Val Leu Tyr Phe Val Met Asp Leu Leu Lys	335	340	345
Asp Met Pro Gly Leu Pro Gly Leu Phe Val Ala Cys Leu Phe Ser	350	355	360
Gly Ser Leu Ser Thr Ile Ser Ser Ala Phe Asn Ser Leu Ala Thr	365	370	375
Val Thr Met Glu Asp Leu Ile Gln Pro Trp Phe Pro Gln Leu Thr	380	385	390
Glu Thr Arg Ala Ile Met Leu Ser Arg Ser Leu Ala Phe Ala Tyr	395	400	405
Gly Leu Val Cys Leu Gly Met Ala Tyr Val Ser Ser His Leu Gly	410	415	420
Ser Val Leu Gln Ala Ala Leu Ser Ile Phe Gly Met Val Gly Gly	425	430	435
Pro Leu Leu Gly Leu Phe Cys Leu Gly Met Phe Phe Pro Cys Ala	440	445	450
Asn Pro Leu Gly Ala Ile Val Gly Leu Leu Thr Gly Leu Thr Met	455	460	465
Ala Phe Trp Ile Gly Ile Gly Ser Ile Val Ser Arg Met Ser Ser	470	475	480
Ala Ala Ala Ser Pro Pro Leu Asn Gly Ser Ser Ser Phe Leu Pro	485	490	495
Ser Asn Leu Thr Val Ala Thr Val Thr Thr Leu Met Pro Ser Thr	500	505	510
Leu Ser Lys Pro Thr Gly Leu Gln Gln Phe Tyr Ser Leu Ser Tyr	515	520	525
Leu Trp Tyr Ser Ala His Asn Ser Thr Thr Val Ile Ala Val Gly	530	535	540
Leu Ile Val Ser Leu Leu Thr Gly Gly Met Arg Gly Arg Ser Leu	545	550	555
Asn Pro Gly Thr Ile Tyr Pro Val Leu Pro Lys Leu Leu Ala Leu	560	565	570
Leu Pro Leu Ser Cys Gln Lys Arg Leu Cys Trp Arg Ser His Asn	575	580	585
Gln Asp Ile Pro Val Val Thr Asn Leu Phe Pro Glu Lys Met Gly	590	595	600
Asn Gly Ala Leu Gln Asp Ser Arg Asp Lys Glu Arg Met Ala Glu	605	610	615
Asp Gly Leu Val His Gln Pro Cys Ser Pro Thr Tyr Ile Val Gln	620	625	630
Glu Thr Ser Leu			



<210> 38  
 <211> 507  
 <212> PRT  
 <213> Homo sapiens

<300>  
 <308> GenBank ID No: g3639058

<400> 38  
 Met Ala Gly Ala Gly Pro Lys Arg Arg Ala Leu Ala Ala Pro Ala  
 1 5 10 15  
 Ala Glu Glu Lys Glu Glu Ala Arg Glu Lys Met Leu Ala Ala Lys  
 20 25 30  
 Ser Ala Asp Gly Ser Ala Pro Ala Gly Glu Gly Glu Gly Val Thr  
 35 40 45  
 Leu Gln Arg Asn Ile Thr Leu Leu Asn Gly Val Ala Ile Ile Val  
 50 55 60  
 Gly Thr Ile Ile Gly Ser Gly Ile Phe Val Thr Pro Thr Gly Val  
 65 70 75  
 Leu Lys Glu Ala Gly Ser Pro Gly Leu Ala Leu Val Val Trp Ala  
 80 85 90  
 Ala Cys Gly Val Phe Ser Ile Val Gly Ala Leu Cys Tyr Ala Glu  
 95 100 105  
 Leu Gly Thr Thr Ile Ser Lys Ser Gly Gly Asp Tyr Ala Tyr Met  
 110 115 120  
 Leu Glu Val Tyr Gly Ser Leu Pro Ala Phe Leu Lys Leu Trp Ile  
 125 130 135  
 Glu Leu Leu Ile Ile Arg Pro Ser Ser Gln Tyr Ile Val Ala Leu  
 140 145 150  
 Val Phe Ala Thr Tyr Leu Leu Lys Pro Leu Phe Pro Thr Cys Pro  
 155 160 165  
 Val Pro Glu Glu Ala Ala Lys Leu Val Ala Cys Leu Cys Val Leu  
 170 175 180  
 Leu Leu Thr Ala Val Asn Cys Tyr Ser Val Lys Ala Ala Thr Arg  
 185 190 195  
 Val Gln Asp Ala Phe Ala Ala Ala Lys Leu Leu Ala Leu Ala Leu  
 200 205 210  
 Ile Ile Leu Leu Gly Phe Val Gln Ile Gly Lys Gly Asp Val Ser  
 215 220 225  
 Asn Leu Asp Pro Lys Phe Ser Phe Glu Gly Thr Lys Leu Asp Val  
 230 235 240  
 Gly Asn Ile Val Leu Ala Leu Tyr Ser Gly Leu Phe Ala Tyr Gly  
 245 250 255  
 Gly Trp Asn Tyr Leu Asn Phe Val Thr Glu Glu Met Ile Asn Pro  
 260 265 270  
 Tyr Arg Asn Leu Pro Leu Ala Ile Ile Ile Ser Leu Pro Ile Val  
 275 280 285  
 Thr Leu Val Tyr Val Leu Thr Asn Leu Ala Tyr Phe Thr Thr Leu  
 290 295 300  
 Ser Thr Glu Gln Met Leu Ser Ser Glu Ala Val Ala Val Asp Phe  
 305 310 315  
 Gly Asn Tyr His Leu Gly Val Met Ser Trp Ile Ile Pro Val Phe  
 320 325 330  
 Val Gly Leu Ser Cys Phe Gly Ser Val Asn Gly Ser Leu Phe Thr

	335	340	345
Ser Ser Arg Leu	Phe Phe Val Gly Ser Arg Glu Gly His Leu Pro		
	350	355	360
Ser Ile Leu Ser	Met Ile His Pro Gln Leu Leu Thr Pro Val Pro		
	365	370	375
Ser Leu Val Phe	Thr Cys Val Met Thr Leu Leu Tyr Ala Phe Ser		
	380	385	390
Lys Asp Ile Phe	Ser Val Ile Asn Phe Phe Ser Phe Phe Asn Trp		
	395	400	405
Leu Cys Val Ala	Leu Ala Ile Ile Gly Met Ile Trp Leu Arg His		
	410	415	420
Arg Lys Pro Glu	Leu Glu Arg Pro Ile Lys Val Asn Leu Ala Leu		
	425	430	435
Pro Val Phe Phe	Ile Leu Ala Cys Leu Phe Leu Ile Ala Val Ser		
	440	445	450
Phe Trp Lys Thr	Pro Val Glu Cys Gly Ile Gly Phe Thr Ile Ile		
	455	460	465
Leu Ser Gly Leu	Pro Val Tyr Phe Phe Gly Val Trp Trp Lys Asn		
	470	475	480
Lys Pro Lys Trp	Leu Leu Gln Gly Ile Phe Ser Thr Thr Val Leu		
	485	490	495
Cys Gln Lys Leu	Met Gln Val Val Pro Gln Glu Thr		
	500	505	

&lt;210&gt; 39

&lt;211&gt; 504

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;300&gt;

&lt;308&gt; GenBank ID No: g1840045

&lt;400&gt; 39

Met Glu Ala Pro Leu Gln Thr Glu Met Val Glu Leu Val Pro Asn	
1 5 10 15	
Gly Lys His Ser Glu Gly Leu Leu Pro Val Ile Thr Pro Met Ala	
20 25 30	
Gly Asn Gln Arg Val Glu Asp Pro Ala Arg Ser Cys Met Glu Gly	
35 40 45	
Lys Ser Phe Leu Gln Lys Ser Pro Ser Lys Glu Pro His Phe Thr	
50 55 60	
Asp Phe Glu Gly Lys Thr Ser Phe Gly Met Ser Val Phe Asn Leu	
65 70 75	
Ser Asn Ala Ile Met Gly Ser Gly Ile Leu Gly Leu Ala Tyr Ala	
80 85 90	
Met Ala Asn Thr Gly Ile Ile Leu Phe Leu Phe Leu Leu Thr Ala	
95 100 105	
Val Ala Leu Leu Ser Ser Tyr Ser Ile His Leu Leu Leu Lys Ser	
110 115 120	
Ser Gly Val Val Gly Ile Arg Ala Tyr Glu Gln Leu Gly Tyr Arg	
125 130 135	
Ala Phe Gly Thr Pro Gly Lys Leu Ala Ala Ala Leu Ala Ile Thr	
140 145 150	

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Leu Gln Asn Ile Gly Ala Met Ser Ser Tyr Leu Tyr Ile Ile Lys
      155                      160                      165
Ser Glu Leu Pro Leu Val Ile Gln Thr Phe Leu Asn Leu Glu Glu
      170                      175                      180
Lys Thr Ser Asp Trp Tyr Met Asn Gly Asn Tyr Leu Val Ile Leu
      185                      190                      195
Val Ser Val Thr Ile Ile Leu Pro Leu Ala Leu Met Arg Gln Leu
      200                      205                      210
Gly Tyr Leu Gly Tyr Ser Ser Gly Phe Ser Leu Ser Cys Met Val
      215                      220                      225
Phe Phe Leu Ile Ala Val Ile Tyr Lys Lys Phe His Val Pro Cys
      230                      235                      240
Pro Leu Pro Pro Asn Phe Asn Asn Thr Thr Gly Asn Phe Ser His
      245                      250                      255
Val Glu Ile Val Lys Glu Lys Val Gln Leu Gln Val Glu Pro Glu
      260                      265                      270
Ala Ser Ala Phe Cys Thr Pro Ser Tyr Phe Thr Leu Asn Ser Gln
      275                      280                      285
Thr Ala Tyr Thr Ile Pro Ile Met Ala Phe Ala Phe Val Cys His
      290                      295                      300
Pro Glu Val Leu Pro Ile Tyr Thr Glu Leu Lys Asp Pro Ser Lys
      305                      310                      315
Lys Lys Met Gln His Ile Ser Asn Leu Ser Ile Ala Val Met Tyr
      320                      325                      330
Ile Met Tyr Phe Leu Ala Ala Leu Phe Gly Tyr Leu Thr Phe Tyr
      335                      340                      345
Asn Gly Val Glu Ser Glu Leu Leu His Thr Tyr Ser Lys Val Asp
      350                      355                      360
Pro Phe Asp Val Leu Ile Leu Cys Val Arg Val Ala Val Leu Thr
      365                      370                      375
Ala Val Thr Leu Thr Val Pro Ile Val Leu Phe Pro Val Arg Arg
      380                      385                      390
Ala Ile Gln Gln Met Leu Phe Pro Asn Gln Glu Phe Ser Trp Leu
      395                      400                      405
Arg His Val Leu Ile Ala Val Gly Leu Leu Thr Cys Ile Asn Leu
      410                      415                      420
Leu Val Ile Phe Ala Pro Asn Ile Leu Gly Ile Phe Gly Val Ile
      425                      430                      435
Gly Ala Thr Ser Ala Pro Phe Leu Ile Phe Ile Phe Pro Ala Ile
      440                      445                      450
Phe Tyr Phe Arg Ile Met Pro Thr Glu Lys Glu Pro Ala Arg Ser
      455                      460                      465
Thr Pro Lys Ile Leu Ala Leu Cys Phe Ala Met Leu Gly Phe Leu
      470                      475                      480
Leu Met Thr Met Ser Leu Ser Phe Ile Ile Ile Asp Trp Ala Ser
      485                      490                      495
Gly Thr Ser Arg His Gly Gly Asn His
      500

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&lt;210&gt; 40

&lt;211&gt; 393

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;300&gt;

&lt;308&gt; GenBank ID No: g1526438

&lt;400&gt; 40

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Met Ala Ala Val Gly Ala Gly Gly Ser Thr Ala Ala Pro Gly Pro
 1           5           10           15
Gly Ala Val Ser Ala Gly Ala Leu Glu Pro Gly Thr Ala Ser Ala
 20           25           30
Ala His Arg Arg Leu Lys Tyr Ile Ser Leu Ala Val Leu Val Val
 35           40           45
Gln Asn Ala Ser Leu Ile Leu Ser Ile Arg Tyr Ala Arg Thr Leu
 50           55           60
Pro Gly Asp Arg Phe Phe Ala Thr Thr Ala Val Val Met Ala Glu
 65           70           75
Val Leu Lys Gly Leu Thr Cys Leu Leu Leu Leu Phe Ala Gln Lys
 80           85           90
Arg Gly Asn Val Lys His Leu Val Leu Phe Leu His Glu Ala Val
 95          100          105
Leu Val Gln Tyr Val Asp Thr Leu Lys Leu Ala Val Pro Ser Leu
110          115          120
Ile Tyr Thr Leu Gln Asn Asn Leu Gln Tyr Val Ala Ile Ser Asn
125          130          135
Leu Pro Ala Ala Thr Phe Gln Val Thr Tyr Gln Leu Lys Ile Leu
140          145          150
Thr Thr Ala Leu Phe Ser Val Leu Met Leu Asn Arg Ser Leu Ser
155          160          165
Arg Leu Gln Trp Ala Ser Leu Leu Leu Leu Phe Thr Gly Val Ala
170          175          180
Ile Val Gln Ala Gln Gln Ala Gly Gly Gly Gly Pro Arg Pro Leu
185          190          195
Asp Gln Asn Pro Gly Ala Gly Leu Ala Ala Val Val Ala Ser Cys
200          205          210
Leu Ser Ser Gly Phe Ala Gly Val Tyr Phe Glu Lys Ile Leu Lys
215          220          225
Gly Ser Ser Gly Ser Val Trp Leu Arg Asn Leu Gln Leu Gly Leu
230          235          240
Phe Gly Thr Ala Leu Gly Leu Val Gly Leu Trp Trp Ala Glu Gly
245          250          255
Thr Ala Val Ala Thr Arg Gly Phe Phe Phe Gly Tyr Thr Pro Ala
260          265          270
Val Trp Gly Val Val Leu Asn Gln Ala Phe Gly Gly Leu Leu Val
275          280          285
Ala Val Val Val Lys Tyr Ala Asp Asn Ile Leu Lys Gly Phe Ala
290          295          300
Thr Ser Leu Ser Ile Val Leu Ser Thr Val Ala Ser Ile Arg Leu
305          310          315
Phe Gly Phe His Val Asp Pro Leu Phe Ala Leu Gly Ala Gly Leu
320          325          330
Val Ile Gly Ala Val Tyr Leu Tyr Ser Leu Pro Arg Gly Ala Ala
335          340          345
Lys Ala Ile Ala Ser Ala Ser Ala Ser Ala Ser Gly Pro Cys Val
350          355          360
His Gln Gln Pro Pro Gly Gln Pro Pro Pro Pro Gln Leu Ser Ser
365          370          375
His Arg Gly Asp Leu Ile Thr Glu Pro Phe Leu Pro Lys Ser Val

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380  
Leu Val Lys

385

390

<210> 41  
<211> 893  
<212> PRT  
<213> Homo sapiens

<300>  
<308> GenBank ID No: g3335175

<400> 41  
His Val Gln Asp Phe Thr Ala Phe Trp Asp Lys Ala Ser Glu Thr  
1 5 10 15  
Pro Thr Leu Gln Gly Leu Ser Phe Thr Val Arg Pro Gly Glu Leu  
20 25 30  
Leu Ala Val Val Gly Pro Val Gly Ala Gly Lys Ser Ser Leu Leu  
35 40 45  
Ser Ala Val Leu Gly Glu Leu Ala Pro Ser His Gly Leu Val Ser  
50 55 60  
Val His Gly Arg Ile Ala Tyr Val Ser Gln Gln Pro Trp Val Phe  
65 70 75  
Ser Gly Thr Leu Arg Ser Asn Ile Leu Phe Gly Lys Lys Tyr Glu  
80 85 90  
Lys Glu Arg Tyr Glu Lys Val Ile Lys Ala Cys Ala Leu Lys Lys  
95 100 105  
Asp Leu Gln Leu Leu Glu Asp Gly Asp Leu Thr Val Ile Gly Asp  
110 115 120  
Arg Gly Thr Thr Leu Ser Gly Gly Gln Lys Ala Arg Val Asn Leu  
125 130 135  
Ala Arg Ala Val Tyr Gln Asp Ala Asp Ile Tyr Leu Leu Asp Asp  
140 145 150  
Pro Leu Ser Ala Val Asp Ala Glu Val Ser Arg His Leu Phe Glu  
155 160 165  
Leu Cys Ile Cys Gln Ile Leu His Glu Lys Ile Thr Ile Leu Val  
170 175 180  
Thr His Gln Leu Gln Tyr Leu Lys Ala Ala Ser Gln Ile Leu Ile  
185 190 195  
Leu Lys Asp Gly Lys Met Val Gln Lys Gly Thr Tyr Thr Glu Phe  
200 205 210  
Leu Lys Ser Gly Ile Asp Phe Gly Ser Leu Leu Lys Lys Asp Asn  
215 220 225  
Glu Glu Ser Glu Gln Pro Pro Val Pro Gly Thr Pro Thr Leu Arg  
230 235 240  
Asn Arg Thr Phe Ser Glu Ser Ser Val Trp Ser Gln Gln Ser Ser  
245 250 255  
Arg Pro Ser Leu Lys Asp Gly Ala Leu Glu Ser Gln Asp Thr Glu  
260 265 270  
Asn Val Pro Val Thr Leu Ser Glu Glu Asn Arg Ser Glu Gly Lys  
275 280 285  
Val Gly Phe Gln Ala Tyr Lys Asn Tyr Phe Arg Ala Gly Ala His  
290 295 300  
Trp Ile Val Phe Ile Phe Leu Ile Leu Leu Asn Thr Ala Ala Gln

	305	310	315
Val Ala Tyr Val	Leu Gln Asp Trp Trp	Leu Ser Tyr Trp Ala	Asn
	320	325	330
Lys Gln Ser Met	Leu Asn Val Thr Val	Asn Gly Gly Gly Asn	Val
	335	340	345
Thr Glu Lys Leu	Asp Leu Asn Trp Tyr	Leu Gly Ile Tyr Ser	Gly
	350	355	360
Leu Thr Val Ala	Thr Val Leu Phe Gly	Ile Ala Arg Ser Leu	Leu
	365	370	375
Val Phe Tyr Val	Leu Val Asn Ser Ser	Gln Thr Leu His Asn	Lys
	380	385	390
Met Phe Glu Ser	Ile Leu Lys Ala Pro	Val Leu Phe Phe Asp	Arg
	395	400	405
Asn Pro Ile Gly	Arg Ile Leu Asn Arg	Phe Ser Lys Asp Ile	Gly
	410	415	420
His Leu Asp Asp	Leu Leu Pro Leu Thr	Phe Leu Asp Phe Ile	Gln
	425	430	435
Thr Leu Leu Gln	Val Val Gly Val Val	Ser Val Ala Val Ala	Val
	440	445	450
Ile Pro Trp Ile	Ala Ile Pro Leu Val	Pro Leu Gly Ile Ile	Phe
	455	460	465
Ile Phe Leu Arg	Arg Tyr Phe Leu Glu	Thr Ser Arg Asp Val	Lys
	470	475	480
Arg Leu Glu Ser	Thr Thr Arg Ser Pro	Val Phe Ser His Leu	Ser
	485	490	495
Ser Ser Leu Gln	Gly Leu Trp Thr Ile	Arg Ala Tyr Lys Ala	Glu
	500	505	510
Glu Arg Cys Gln	Glu Leu Phe Asp Ala	His Gln Asp Leu His	Ser
	515	520	525
Glu Ala Trp Phe	Leu Phe Leu Thr Thr	Ser Arg Trp Phe Ala	Val
	530	535	540
Arg Leu Asp Ala	Ile Cys Ala Met Phe	Val Ile Ile Val Ala	Phe
	545	550	555
Gly Ser Leu Ile	Leu Ala Lys Thr Leu	Asp Ala Gly Gln Val	Gly
	560	565	570
Leu Ala Leu Ser	Tyr Ala Leu Thr Leu	Met Gly Met Phe Gln	Trp
	575	580	585
Cys Val Arg Gln	Ser Ala Glu Val Glu	Asn Met Met Ile Ser	Val
	590	595	600
Glu Arg Val Ile	Glu Tyr Thr Asp Leu	Glu Lys Glu Ala Pro	Trp
	605	610	615
Glu Tyr Gln Lys	Arg Pro Pro Pro Ala	Trp Pro His Glu Gly	Val
	620	625	630
Ile Ile Phe Asp	Asn Val Asn Phe Met	Tyr Ser Pro Gly Gly	Pro
	635	640	645
Leu Val Leu Lys	His Leu Thr Ala Leu	Ile Lys Ser Gln Glu	Lys
	650	655	660
Val Gly Ile Val	Gly Arg Thr Gly Ala	Gly Lys Ser Ser Leu	Ile
	665	670	675
Ser Ala Leu Phe	Arg Leu Ser Glu Pro	Glu Gly Lys Ile Trp	Ile
	680	685	690
Asp Lys Ile Leu	Thr Thr Glu Ile Gly	Leu His Asp Leu Arg	Lys
	695	700	705
Lys Met Ser Ile	Ile Pro Gln Glu Pro	Val Leu Phe Thr Gly	Thr
	710	715	720

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Met Arg Lys Asn Leu Asp Pro Phe Lys Glu His Thr Asp Glu Glu
      725      730      735
Leu Trp Asn Ala Leu Gln Glu Val Gln Leu Lys Glu Thr Ile Glu
      740      745      750
Asp Leu Pro Gly Lys Met Asp Thr Glu Leu Ala Glu Ser Gly Ser
      755      760      765
Asn Phe Ser Val Gly Gln Arg Gln Leu Val Cys Leu Ala Arg Ala
      770      775      780
Ile Leu Arg Lys Asn Gln Ile Leu Ile Ile Asp Glu Ala Thr Ala
      785      790      795
Asn Val Asp Pro Arg Thr Asp Glu Leu Ile Gln Lys Lys Ile Arg
      800      805      810
Glu Lys Phe Ala His Cys Thr Val Leu Thr Ile Ala His Arg Leu
      815      820      825
Asn Thr Ile Ile Asp Ser Asp Lys Ile Met Val Leu Asp Ser Gly
      830      835      840
Arg Leu Lys Glu Tyr Asp Glu Pro Tyr Val Leu Leu Gln Asn Lys
      845      850      855
Glu Ser Leu Phe Tyr Lys Met Val Gln Gln Leu Gly Lys Ala Glu
      860      865      870
Ala Ala Ala Leu Thr Glu Thr Ala Lys Gln Val Ile Leu Gln Lys
      875      880      885
Lys Leu Ser Thr Tyr Trp Ser His
      890

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&lt;210&gt; 42

&lt;211&gt; 453

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;300&gt;

&lt;308&gt; GenBank ID No: g1279457

&lt;400&gt; 42

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Met Ala Leu Arg Gly Phe Cys Ser Arg Trp Leu Arg Pro Ala Leu
  1      5      10      15
Ala Ile Gly Leu Phe Ala Ser Met Ala Ala Val Leu Leu Gly Gly
      20      25      30
Ala Arg Ala Ser Arg Leu Leu Phe Gln Arg Leu Leu Trp Asp Val
      35      40      45
Val Arg Ser Pro Ile Ser Phe Phe Glu Arg Thr Pro Ile Gly His
      50      55      60
Leu Leu Asn Arg Phe Ser Lys Glu Thr Asp Thr Val Asp Val Asp
      65      70      75
Ile Pro Asp Lys Leu Arg Ser Leu Leu Met Tyr Ala Phe Gly Leu
      80      85      90
Leu Glu Val Ser Leu Val Val Glu Trp Pro Thr Pro Leu Pro Leu
      95      100      105
Trp Pro Ser Cys His Cys Phe Ser Ser Thr Leu Gly Phe Arg Trp
      110      115      120
Leu Ala Ala Asn Val Glu Leu Leu Gly Asn Gly Leu Val Phe Ala
      125      130      135
Ala Ala Thr Cys Ala Val Leu Ser Lys Ala His Leu Ser Ala Gly
      140      145      150

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Leu Val Gly Phe Ser Val Ser Ala Ala Leu Gln Val Thr Gln Thr	155	160	165
Leu Gln Trp Val Val Arg Asn Trp Thr Asp Leu Glu Asn Ser Ile	170	175	180
Val Ser Val Glu Arg Met Gln Asp Tyr Ala Trp Thr Pro Lys Glu	185	190	195
Ala Pro Trp Arg Leu Pro Thr Cys Ala Ala Gln Pro Pro Trp Pro	200	205	210
Gln Gly Gly Gln Ile Glu Phe Arg Asp Phe Gly Leu Arg Tyr Arg	215	220	225
Pro Glu Leu Pro Leu Ala Val Gln Gly Val Ser Phe Lys Ile His	230	235	240
Ala Gly Glu Lys Val Gly Ile Val Gly Arg Thr Gly Ala Gly Lys	245	250	255
Ser Ser Leu Ala Ser Gly Leu Leu Arg Leu Gln Glu Ala Ala Glu	260	265	270
Gly Gly Ile Trp Ile Asp Gly Val Pro Ile Ala His Val Gly Val	275	280	285
His Thr Leu Arg Ser Arg Ile Ser Ile Ile Pro Gln Asp Pro Ile	290	295	300
Leu Phe Pro Gly Ser Leu Arg Met Asn Leu Asp Leu Leu Gln Glu	305	310	315
His Ser Asp Glu Ala Ile Trp Ala Ala Leu Glu Thr Val Gln Leu	320	325	330
Lys Ala Leu Val Ala Cys Leu Pro Gly Gln Leu Gln Tyr Lys Cys	335	340	345
Ala Asp Arg Gly Glu Asp Leu Ser Val Gly Gln Lys Gln Leu Leu	350	355	360
Cys Leu Ala Arg Ala Leu Leu Arg Lys Thr Gln Ile Leu Ile Leu	365	370	375
Asp Glu Ala Thr Ala Ala Val Asp Pro Gly Thr Glu Leu Gln Met	380	385	390
Gln Ala Met Leu Gly Ser Trp Phe Ala Gln Cys Thr Val Leu Leu	395	400	405
Ile Ala His Arg Leu Arg Ser Val Met Asp Cys Ala Arg Val Leu	410	415	420
Val Met Asp Lys Gly Gln Val Ala Glu Ser Gly Ser Pro Ala Gln	425	430	435
Leu Leu Ala Gln Lys Gly Leu Phe Tyr Arg Leu Ala Gln Glu Ser	440	445	450
Gly Leu Val			